SCIENTIFIC DISCUSSION

1. Introduction

Worldwide there are currently approximately 40 million persons living with human immunodeficiency virus-1 (HIV-1) or acquired immunodeficiency syndrome (AIDS). Of these, over 700,000 people are living within the EU, Norway and Iceland.

The goal of antiretroviral therapy for HIV-1 infection is to delay disease progression and increase the duration of survival by achieving maximal and prolonged suppression of HIV-1 replication. The standard of care for treatment involves the use of a combination of antiretroviral agents, typically a combination of at least three active substances, including a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) and two active substances from the nucleoside reverse transcriptase inhibitor/nucleotide reverse transcriptase inhibitor class (NRTI/NtRTI).

Antiretroviral regimens might imply a high pill burden and a frequency of administration hardly compatible with the patient's daily life. Furthermore, to achieve successful long-term treatment, the prevention of drug resistance has become the most significant challenge. Incomplete adherence to antiretroviral regimens is an important factor contributing to the development of viral resistance and treatment failure. Therefore, there continues to be a need for new treatments that combine potent and sustained efficacy with acceptable tolerability and minimal long-term toxicity, as well as practical and convenient dosing regimens.

Atripla contains a fixed-dose combination of three active substances: efavirenz (an NNRTI), emtricitabine (an NRTI), and tenofovir disoproxil (as fumarate, an NtRTI). It is intended to provide combination antiretroviral therapy for administration as a single, once-daily tablet for the treatment of HIV-1 infected adults.

The rationale for the development of this fixed dose combination is that the individual active substances have shown to be potent and selective inhibitors of HIV-1 reverse transcriptase (RT) and that their combined use is recommended in national and international HIV-1 infection treatment guidelines (e.g. national European guidelines, US guidelines and WHO guidelines) due to a lack of cross-resistance, dual antagonism and significant overlap in toxicities, respectively. The fixed combination hence aims to simplify regimens and to improve adherence to therapy.

A so-called 'application for fixed combination medicinal product' has been submitted for Atripla. All individual substances of Atripla are authorised in the EEA via a Community procedure: efavirenz as Sustiva/Stocrin (EU/1/98/110/001-009, EU/1/99/111/001-009), emtricitabine as Emtriva (EU/1/03/261/001-003), and tenofovir disoproxil fumarate as Viread (EU/1/01/200/001). Moreover, the fixed-combination of emtricitabine and tenofovir DF has been approved as Truvada (EU/1/04/305/001). The Marketing Authorisation Holders for all above-mentioned medicinal products authorised the applicant for Atripla to make cross-reference to data previously submitted to these Marketing Authorisations and authorised the EMEA and the CHMP including their experts to refer to and review any data previously submitted to the above-mentioned Marketing Authorisations as required for the review of the Marketing Authorisation Application for Atripla.

The applicant did apply for accelerated assessment of the application. The CHMP did not accept the request for accelerated assessment as the applicant's argumentation did not provide evidence that the triple combination meets an unmet medical need. The difference between two tablets once daily to one tablet daily was not necessarily regarded as clinically meaningful and none of the references provided by the applicant did investigate this issue hence the claimed impact could not be quantified in medical epidemiological terms. Furthermore, a bioequivalence trial, which was the pivotal basis of the initial application, could not be used to identify a clear advantage in terms of a clinically relevant benefit over existing therapies. Based on the claims and description of the available data provided by the applicant, it was not possible to assume that the product will be of major public health interest.

Atripla is available in film-coated tablets containing 600 mg efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate). The recommended dose is one tablet taken orally once daily on an empty stomach at bedtime.

The claimed indication read as follows: "Atripla is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for use alone as a single tablet regimen or in combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults."

The approved indication is:

> "Atripla is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Atripla prior to initiation of their first antiretroviral treatment regimen (see sections 4.4 and 5.1).
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> The demonstration of the benefit of Atripla is primarily based on 24-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to Atripla (see section 5.1). No data are currently available from clinical studies with Atripla in treatment-naïve or in heavily pretreated patients.
>
> No data are available to support the combination of Atripla and other antiretroviral agents."

2. Quality aspects

Introduction

Atripla is presented as film-coated tablets containing a fixed combination of 600 mg of efavirenz, 200 mg emtricitabine and 245 mg of tenofovir disoproxil (as fumarate), equivalent to 136 mg of tenofovir. The other ingredients include croscarmellose sodium, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, sodium lauril sulphate, purified water and colorants. The film coat consists of black iron oxide, macrogol, polyvinyl alcohol, red iron oxide, talc and titanium dioxide.

The tablets are packed in an HDPE bottle containing silica gel desiccant and a polypropylene continuous-thread child resistant cap with an induction activated aluminium foil.

Active Substances

Three active substances are used in this fixed combination product, efavirenz, emtricitabine and tenofovir disoproxil.

Efavirenz

Its chemical name is (S)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1 benzoxazin-2-one according to the IUPAC nomenclature. Efavirenz is a white to slightly pink crystalline powder and it is soluble in various organic solvents but insoluble in water. The above-mentioned active substance has one chiral centre and is used as a single enantiomer (S).

Manufacture

Efavirenz can be synthesised in two or four reactions steps. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls

included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented.

Structure elucidation has been performed by ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, ultraviolet spectroscopy, infrared absorption spectroscopy, elemental analysis, and mass spectroscopy. The proposed molecular structure was confirmed by single-crystal X-ray analysis of the (-)-camphanic imide derivative of efavirenz.

The molecular weight was determined by elemental analysis which is in agreement with the expected molecular weight.

Specification

The efavirenz specifications include tests for appearance, identification (UV, IR, HPLC), assay, impurities (HPLC), heavy metals (Ph.Eur.), Residue on ignition (Ph.Eur.), completeness and clarity of solution (Ph.Eur.), particle size, water content (Karl-Fisher), specific rotation (Ph.Eur.) and residual solvents (GC).

It was verified that all specifications reflect the relevant quality attributes of the efavirenz. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.

Impurities were described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

Stability

The stability results from long-term, accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of the efavirenz. This active substance is susceptible to degradation under the influence of light since the discoloration of the surface of the active substance and increase of an impurity was observed during a photostability study. Therefore, the active substance requires protection from light. The results of the long-term and accelerated studies fulfil the proposed specification and for that reason support the proposed retest period.

Emtricitabine

The chemical name of emtricitabine is 5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine according to the IUPAC nomenclature. It is a white to off-white powder and it is freely soluble in various aqueous solutions, slightly soluble in acetonitrile and very slightly soluble in isopropyl acetate.

- **Manufacture**

Emtricitabine can be synthesised in three reactions steps including two alternative options. Comparative batch analysis data for this active substance produced by the 2 processes show that the physical properties of the active substance remain unchanged. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. Furthermore, it was confirmed that the impurity profile of emtricitabine synthesised by the both processes has been fully characterised.

Structure elucidation has been performed by infrared absorption, ultraviolet spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy and mass spectroscopy. The proposed molecular structure was confirmed by single-crystal X-ray analysis.

- **Specification**

The emtricitabine specification include tests for appearance, identification (IR and HPLC), clarity of solution, water content (Ph.Eur), enantiomeric purity, assay, impurities, heavy metals (PhEur), residue on ignition (PhEur), residual solvents and particle size.

It was verified that all specifications for this particular active substance reflect the relevant quality attributes of emtricitabine. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.

Impurities were well described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided. Furthermore, all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of emtricitabine. It was confirmed that this active substance is not susceptible to degradation under the influence of light. Therefore, it can be concluded that emtricitabine is not sensitive to light and does not require protection from light. The results of the long-term and accelerated studies fulfil the proposed specification and for that reason support the agreed retest period.

Tenofovir Disoproxil Fumarate

The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2-[[Bis[(isopropoxycarbonyl)oxy]methoxy]-phosphinyl]methoxy]propyl]adenine fumarate (1:1) according to the IUPAC nomenclature. Tenofovir disoproxil fumarate is a white to off-white crystalline powder and it is freely soluble in dimethylformamide, soluble in methanol, acid hydrochloride (0.1 N HCL), ethanol, sparingly soluble in acetone, isopropanol, water, slightly soluble in acetonitrile, ethyl acetate, insoluble in dichloromethane, hexane, diethyl ether, di-n-butyl ether, isopropylether. The above-mentioned active substance has one chiral centre and is used as a single enantiomer (R).

- **Manufacture**

Tenofovir disoproxil fumarate is synthesised in four reactions steps. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. Structure elucidation has been performed by infrared absorption spectroscopy, ultraviolet spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, ^{31}P-NMR spectroscopy, mass spectroscopy and elemental analysis.

The proposed molecular structure was confirmed by X-ray single crystal structural analysis.

- **Specification**

The tenofovir disoproxil fumarate specifications include tests for appearance, identification (IR, HPLC), clarity of solution, water content (Ph.Eur.), enantiomeric purity, assay, Impurities (HPLC), fumaric acid content, heavy metals (Ph.Eur.), residual solvents, particle size and differential scanning calorimetry.

Impurities were described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the

relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of the tenofovir disoproxil fumarate. The results of the photostability testing confirm that the active substance is not susceptible to degradation under the influence of light. In this context, no protection from light is needed. The results of the long-term and accelerated studies fulfil the proposed specification and for that reason support the agreed retest period and storage conditions.

Medicinal Product

Pharmaceutical Development

All information regarding the choice of the drug substance and the excipients are sufficiently justified. The proposed medicinal product combining the currently approved doses of efavirenz, emtricitabine and tenofovir disoproxil fumarate into a single tablet to be administered once daily intends to support patient adherence to treatment. In this context, the aim of the pharmaceutical development was to develop a single formulation containing 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate, such that the physical and chemical properties of each active substance could be accommodated. Furthermore, the objectives in the development of this formulation was to develop a formulation with high drug load, minimize physical and chemical interactions, ensure adequate chemical stability of the drug product and of the active substances, develop a robust formulation and an efficient manufacturing process.

In this context, distinct manufacturing process approaches and different formulations containing slightly different excipients were investigated and optimised. Having investigated different formulations and taken into account the physical and chemical properties of each of the active substances, the manufacturing process selected involves the preparation of a wet granulation of efavirenz and a dry granulation of emtricitabine and tenofovir disoproxil fumarate. The granulations are blended separately with extra-granular magnesium stearate, compressed into bilayer tablets, and then film-coated. Process optimization studies were conducted in order to establish critical process parameters for the wet granulation of efavirenz, dry granulation of emtricitabine/tenofovir, bilayer tablet compression, and aqueous film-coating operations.

Furthermore, a particular challenge was to develop a suitable dissolution methodology which would be discriminatory for each active substance in the product, when linked to *in vivo* parameters taken from bioequivalence studies with different formulations. Some investigations have been performed to evaluate the discriminatory power of the dissolution method. However, the current dissolution method conditions for the quality control of the drug product are not considered as sufficiently suitable to ensure batch to batch consistency and to ensure that future batches have the same quality in terms of dissolution than the biobatch used in the relevant bioequivalent study. The conditions of the dissolution method for routine quality control should be improved in order to obtain an optimal discriminating in-vitro dissolution method for all of the three drug substances.

Manufacture of the Product

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as wet granulation, dry granulation, milling, blending, compressing and film coating. Furthermore, the equipment used is commonly available in the pharmaceutical industry. The manufacturing process including intermediate products and critical steps were adequately validated.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

Product Specification

The proposed release and shelf life specifications provided contain the quality relevant characteristics required for this pharmaceutical form. Furthermore, they were established according the ICH guidelines and include the following tests: appearance, identification (HPLC, TLC), water content (Karl Fischer), assay, degradation product content, content uniformity (HPLC) and dissolution.

All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.

The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

Stability of the Product

The stability studies were conducted according to the relevant ICH guidelines. Three primary batches of the drug product have been stored at long term, intermediate and accelerated conditions in the proposed market packaging.

One production batch was stored under elevated temperature conditions for 3 months and at ICH conditions, another production batch was stored under high temperature and humidity conditions for 3 months and finally another production batch was stored for photostability at ICH conditions.

Based on the available stability data, the proposed shelf life of 24 months and the storage precautions "Store in the original package. Keep the bottle tightly closed." as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Overall, information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. A particular challenge in the pharmaceutical development of this product has been how to balance the different physicochemical attributes of three different active substances in one formulation. Furthermore, the development of a suitably-discriminating dissolution test for all active substances has presented a particularly difficult challenge. At the time of the CHMP Opinion, this methodology had not been completely optimised and should be therefore improved. Therefore, the applicant was required to give an assurance that the methodology would be optimised in a satisfactory manner post-authorisation, in the form of a follow-up measure, to be resolved within an agreed timeframe.

3. Non-clinical aspects

Introduction

The rationale for the fixed combination of efavirenz, emtricitabine and tenofovir DF is to simplify HIV-treatment regimens and to improve adherence to therapy by providing combination antiretroviral therapy for administration as a single, once-daily tablet. The individual active substances are already approved to be used together in combination therapy of HIV-1 infected patients. The Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (CHMP/EMEA/CHMP/SWP/258498/2005, draft) recognises the principal need to design the non-clinical study programme for a fixed combination depending on the available data for the compounds to be combined as well as the intended clinical use.

Comprehensive non-clinical study programmes have been performed for efavirenz, emtricitabine and tenofovir DF. The applicant claimed that all definitive non-clinical toxicity and toxicokinetic studies of these programmes were conducted in accordance with applicable guidelines and under GLP conditions.

No additional non-clinical safety studies have been performed that were relevant for the assessment of the fixed-combination of efavirenz, emtricitabine and tenofovir DF. The above-mentioned draft guideline on non-clinical development programmes for fixed combinations states that safety studies in animals are in general not required when the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use. Furthermore, the Note for Guidance on Fixed Combination Medicinal Products (CHMP/EWP/240/95) specifies that in the case of combinations for long term use safety studies in animals will not be required when safety data on 300-600 patients for six month or longer are available.

In national and international HIV-1 infection treatment guidelines (e.g. national European guidelines, US guidelines and WHO guidelines) efavirenz in combination with emtricitabine or lamivudine and tenofovir DF is recommended as a preferred regimen for initial therapy. Furthermore, data from the following clinical studies investigating the combined use of the three active substances is presented in the section "Clinical aspects":

- 144-week and 168-week data from study GS-01-934;
- 24-week data from study GS-US-164-0107;
- 24-week data from study AI266073.

Furthermore, supportive data from the clinical study GS-99-903 investigating a combination of lamivudine (which in principle can be considered very similar to emtricitabine) together with efavirenz and tenofovir DF was provided. Also there is post-marketing data from the individual components of the triple combination as well as from the fixed combination itself.

Due to this sufficiently documented clinical evidence of the use of efavirenz, emtricitabine and tenofovir DF in combination for the treatment of HIV-1 infection the CHMP considered the lack of additional non-clinical safety studies for the fixed combination justified.

Pharmacology

- Primary pharmacodynamics / Secondary pharmacodynamics

The mechanisms of action and the effects of efavirenz, emtricitabine and tenofovir DF have been extensively investigated and are well-established. All three active substances are potent and selective inhibitors of HIV-1, weak inhibitors of human DNA polymerases, and show low potential to induce mitochondrial toxicity:

- ***Efavirenz*** (EFV) is a non-nucleoside reverse transcriptase inhibitor of HIV-1. Its activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase. HIV-2 and human cell polymerases α, β, γ, and δ are not inhibited by efavirenz.
- ***Emtricitabine*** (FTC) is a synthetic nucleoside analogue of cytidine that is very similar in structure to lamivudine (3TC). After phosphorylation via phosphorylases in T-cells and in non-dividing monocytic cells, emtricitabine triphosphate (FTC-TP) acts to competitively inhibit HIV-1 reverse transcriptase and functions as a chain terminator. Emtricitabine triphosphate is able to inhibit the viral polymerases of HIV-1, HIV-2 and hepatitis B virus (HBV). It has been investigated clinically for the treatment of chronic HBV infection.
- ***Tenofovir*** is provided for clinical use as the fumaric acid salt of the disoproxil ester derivative of tenofovir (TDF). Tenofovir itself is an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5'-monophosphate. The negative charge on tenofovir at neutral pH limits its oral bioavailability, hence its provision as a pro-drug that is rapidly converted to tenofovir after absorption. Tenofovir is metabolised intracellularly to the active diphosphate form, which acts as a competitive inhibitor of HIV-1 reverse transcriptase. The active moiety is also able to inhibit the viral polymerases of HIV-2 and HBV.

Emtricitabine and tenofovir are phosphorylated intracellularly through non-overlapping pathways and in combination show no antagonism for the formation of their active metabolites. The combination of efavirenz with emtricitabine, efavirenz with tenofovir, and emtricitabine with tenofovir, respectively, all show additive to synergistic anti-HIV-1 activity in vitro. With respect to the drug resistance aspects of the use of the triple combination product, in vitro studies have shown no cross-resistance between the NRTI-associated substitutions M184V/I and/or K65R and efavirenz nor any cross-resistance between efavirenz-associated substitutions and either emtricitabine or tenofovir. The clinical resistance data (see section "Clinical aspects") correspond with the in vitro resistance selection data which showed selection of efavirenz and emtricitabine resistance, and more delayed selection of tenofovir resistance among the subset of patients with virologic failure.

In the light of this available knowledge as well as the sufficiently documented clinical experience with the combination of these active substances the CHMP considered it justified that no further pharmaco-dynamic data for the combination was provided.

- Safety pharmacology programme

Safety pharmacology studies performed for the individual components of Atripla did not show significant unwanted pharmacological activity. No additional safety pharmacology studies were performed with the combination of efavirenz, emtricitabine and tenofovir DF. Due to the available data for the components and considering the extensive clinical use of this combination, this was considered justified by the CHMP.

- Pharmacodynamic drug interactions

A pharmacodynamic drug interaction study was conducted with efavirenz in MT-2 cells investigating the in vitro combination of efavirenz with 12 approved antiretroviral substances not previously examined as well as the anti-HBV substance adefovir and anti-HCV substance ribavirin. The objective was to assess the antiviral effects and cytotoxicity of efavirenz when paired individually with these other substances.

The results showed synergistic-to-additive effects of efavirenz with emtricitabine and tenofovir as well as 8 of the remaining 12 antiretrovirals and adefovir. Data with ritonavir and abacavir suggested potential synergy whereas the results with enfuvirtide suggested additivity. Tests with ribavirin revealed no effect on the potency of efavirenz in HIV antiviral assays. No enhanced cytotoxic effects were observed in any of the combinations used for this study. The results of this study suggest no antagonism with respect to antiviral efficacy for combinations of efavirenz with the antiretroviral substances amprenavir, indinavir, lopinavir, ritonavir, saquinavir, abacavir, emtricitabine, stavudine, tenofovir, zalcitabine, delavirdine and enfuvirtide, as well as with adefovir and ribavirin.

Previous *in vitro* studies investigating the anti-HIV activity of tenofovir and emtricitabine in combination have shown synergistic anti HIV-1 activity. Using the LAI strain of HIV-1 at a multiplicity of infection (MOI) of 0.03 in MT-2 cells, there was demonstrable synergy between tenofovir and emtricitabine in an isobologram analysis; using the LAI strain and a clinical HIV-1 recombinant containing a wild-type RT and protease gene (MM-317) each at MOIs of 0.03 and 0.1, different analyses all showed that the combination was synergistic and the isobologram analysis gave p-values ≤ 0.0017 for all infections.

Pharmacokinetics

A comprehensive nonclinical programme investigating the absorption, distribution, metabolism, excretion and drug interaction potential of efavirenz, emtricitabine, and tenofovir/tenofovir DF has been conducted:

- ***Efavirenz*** (EFV): Following single oral administration to rats (10, 40, and 60 mg/kg) and rhesus monkeys (2, 10, 40, 80 and 120 mg/kg) the pharmacokinetic profile of efavirenz is linear in terms of C_{max} while the increase in AUC is more than dose-proportional. The oral

bioavailability calculated in rats and monkeys is 16% and 42%, respectively. Efavirenz is highly bound to plasma proteins, with a mean free fraction of 0.58% in rat, 0.57% in rhesus monkey and 0.25-0.5% in human plasma. Efavirenz distributes rapidly and extensively in rats after oral dosing; it crosses the placenta and is excreted in milk. The concentration of efavirenz in cerebrospinal fluid (CSF) showed dose-dependent increases in one monkey study. The CSF/plasma ratios ranged from 0.54% to 0.96%, which are comparable to the free unbound fraction in plasma in rat and rhesus monkey. The metabolism of efavirenz is extensive through cytochrome P450 with the major isoenzymes being CYP2B, CYP3A, CYP2B6 and CYP3A4. *In vivo* and *in vitro* metabolism studies have shown that all the efavirenz metabolites identified in humans are also found in rats and cynomolgus monkeys. The major inactive metabolites identified in the three species are the 8-hydroxy efavirenz and its glucuronide conjugate. The plasma half-life of efavirenz in rats is approximately 0.8 to 1 hours compared to more than 40 hours in humans. Excretion in urine and faeces is comparable after an oral dose of 75 mg/kg in monkeys. In rats, low doses of 10 mg/kg were primarily excreted in faeces, while after an oral dose of 250 mg/kg urinary excretion increased almost to the same levels as faecal excretion.

- ***Emtricitabine*** (FTC): Emtricitabine was rapidly and extensively absorbed in mice, rats and cynomolgus monkeys with oral bioavailability ranging from 58 % to 97 % and T_{max} values of 0.5 to 2.5 hours over the dose range of 10 to 600 mg/kg. The pharmacokinetic profile after repeated doses administration was similar to that after single dose administration without any sign of accumulation. The volume of distribution were high and similar across species. Binding to plasma proteins was low (4%). Emtricitabine showed limited penetration to central nervous system with levels reaching 5 to 10% those in the plasma. Studies in pregnant mice and rabbits demonstrated that it crossed the placenta barrier. Foetal/maternal exposure ratios were about 0.4 in both species. Elimination was nearly complete 72 hours after dosing. An average of 67-79 % of the dose was excreted in the urine after oral dosing and mainly as unchanged parent compound (about 90 %). The metabolites appeared to be almost exclusively cleared by renal excretion since only trace (<1% of the applied dose) were found in faeces. Metabolism was similar across species and the principal metabolite identified was a 3'-sulfoxide diastereomers, accounting for approximately 2% of the dose in mice, 2.6% in rats and 6-11% in monkeys. Emtricitabine is actively secreted by renal tubules into the urine.
- ***Tenofovir disoproxil fumarate*** (TDF): Following oral administration, rapid absorption of tenofovir DF was observed with a maximum tenofovir plasma concentration within 0.25 to 1.5 hours post dose. The observed terminal half-life values (biphasic elimination) were approximately 7, 9 and 60 hours in rats, monkeys and dogs respectively. The bioavailability of tenofovir DF was moderate and dependent of the species (10-20 % in rodents and 30-40 % in dogs and monkeys). It also depended on the co-administration of food as food increased the absorption, as well as partially on the dose as it decreased with increasing doses. The volume of distribution was high in all species (more than 1.0 l/kg), suggesting that tenofovir distributes widely. Tenofovir did not appear to cross the brain barrier but crossed the placenta in monkeys. The protein binding was not evaluated in animals, but was found to be low in human plasma. Tenofovir DF was rapidly converted into tenofovir in plasma and liver, much more slowly in intestine. Tenofovir was metabolised intracellularly to tenofovir diphosphate with a $T_{1/2}$ over 50 hours in monkeys PBMCs. *In vitro*, tenofovir disoproxil, tenofovir soproxil and tenofovir were detected, with tenofovir soproxil being the major metabolite observed intracellular. Following oral administration of tenofovir DF in rats and dogs, tenofovir disoproxil was metabolised by non specific esterases to tenofovir. No other metabolites than tenofovir and tenofovir soproxil were detected. *In vitro*, tenofovir DF did not have any inhibiting or inducing effect on CYP3A4, 2D6, 2C9, 2E1 and 1A2. However it induced CYP 1A1 and 2B. In all species, the primary route of elimination was renal, mainly as unchanged substance.

No additional formal nonclinical pharmacokinetic studies were considered warranted by the CHMP with the combination of efavirenz, emtricitabine and tenofovir DF in view of the results of extensive non-clinical studies as well as the clinical pharmacokinetic data for all components.

Limited pharmacokinetic information has been generated as part of a study investigating the pharmacokinetic profiles of various formulations of the fixed combination, which was part of the formulation development. In this non-GLP study the tablets were administered orally to non-naïve beagle dogs dosed approximately weekly for 60 weeks (Phase 1) or naïve beagle dogs for 19 weeks (Phase 2). Dogs in Phase 1 received varying combinations of prototype or commercial formulations containing efavirenz at 600 mg, emtricitabine at 200 mg, and/or tenofovir DF at 300 mg, or lower doses of the agents at 150 mg of efavirenz, 50 mg of emtricitabine and/or 75 mg tenofovir DF. Dogs in Phase 2 received only the lower dose formulations.

For the commercial formulation, maximal plasma concentrations were 323 ± 166, 1790 ± 698, and 423 ± 292 ng/mL at 1.92 ± 2.13, 1.46 ± 0.78, and 1.02 ± 0.43 hr, respectively; the $AUC_{0\text{-last}}$ was 1692 ± 895, 8295 ± 2714, and 1622 ± 755 ng•hr/mL for efavirenz, emtricitabine and tenofovir DF, respectively. At the lower doses used in this study (150 mg of efavirenz, 50 mg of emtricitabine and 75 mg of tenofovir DF), the exposure in dogs to emtricitabine and tenofovir was similar to that in patients while the exposure of efavirenz was ≥ 15-fold lower than that of human patients at steady-state.

Toxicology

The data of a comprehensive nonclincal programme characterising the toxicologic properties of the three compounds efavirenz, emtricitabine and tenofovir / tenofovir DF has been provided. No additional toxicology studies with the combination of efavirenz, emtricitabine and tenofovir DF were considered warranted by the CHMP in view of the results of extensive non-clinical studies as well as the available clinical data.

- Single dose toxicity / Repeat dose toxicity

The acute toxicity of all three active substances is low.

The most prominent toxicologic findings for ***efavirenz*** were nephrotoxicity in rats and biliary changes in rats and monkeys. Non-sustained convulsions were observed in some monkeys receiving efavirenz for ≥ 1 year, at doses yielding plasma AUC values in individual animals that were 4 to 13-fold greater than those in humans given the recommended dose. Biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for ≥ 1 year at a dose resulting in mean AUC values approximately 2-fold greater than those in humans given the recommended dose. The biliary hyperplasia regressed upon cessation of dosing. Biliary fibrosis has been observed in rats. In addition, there were thyroid follicular cell hypertrophy in monkeys, increases in serum transaminase values, without consistent occurrence of hepatocellular necrosis, in monkeys and mice, and increased coagulation parameter values, without evidence of gross or microscopic bleeding in rats and monkeys.

Effects associated with the administration of ***emtricitabine*** in the toxicology studies were confined to high-dose groups. Changes in RBC parameters, interpreted as mild anemia occurred at the highest dose in several studies.

Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. Evidence of renal toxicity was noted in 4 animal species administered tenofovir and tenofovir DF. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2-20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Administration of the tenofovir DF/emtricitabine tablet did not exacerbate the known toxicities of the individual agents, as demonstrated in a 14-day rat toxicology study.

- Genotoxicity

The individual substances efavirenz, emtricitabine and tenofovir DF have been sufficiently tested for genotoxicity *in vitro* and *in vivo*. Efavirenz and emtricitabine exhibit no indication for mutagenic potential. Tenofovir was mutagenic in the *in vitro* mouse lymphoma assay, weakly positive in an unscheduled DNA synthesis test and generally negative in *in vitro* bacterial mutagenicity tests (Ames test). *In vitro* testing of emtricitabine/tenofovir combinations in AMES and Mouse lymphoma assay revealed no evidence for additive mutagenic effects.

Additive mutagenic effects for the combination therapy are not expected and hence the lack of data specific for the fixed combination was considered acceptable.

- Carcinogenicity

In long term carcinogenicity studies of emtricitabine, no drug-related increases in tumour incidence were found in rats and mice.

Carcinogenicity studies have been performed in mice and rats with efavirenz. In rats, no increases in tumour incidence above control were observed. In female mice, incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in all doses. The mechanism of the carcinogenic potential in female mice is unknown.

Long term carcinogenicity study in rats with tenofovir DF did not show any carcinogenic potential. Mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations in the gastrointestinal tract at the highest dose of 600 mg/kg.

Additional carcinogenicity studies with the fixed combination were not considered necessary by the CHMP due to the available non-clinical data for the individual compounds. These data are adequately described in section 5.3 of the SmPC.

- Reproduction Toxicity

Efavirenz induced fetal resorption in rats. Malformations were observed in 3 of 20 fetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. No malformations were observed in fetuses from efavirenz-treated rats and rabbits.

There was no evidence of reproductive toxicity in the studies performed with emtricitabine.

In a peri-natal study performed in rats with tenofovir DF, effects occurred at exposure levels above those likely to be achieved in humans. No adverse effects were seen in rabbits.

The lack of specific studies with the fixed combination was considered justified by the CHMP as the reproductive toxicity profiles of the single substances are already known and as these have been adequately reflected in section 5.3 of the SmPC.

- Local tolerance

No specific studies were considered necessary by the CHMP in the light of the available nonclinical data as well as the clinical evidence submitted for the various components alone or in combination.

- Other toxicity studies

Through the above-mentioned non-GLP study in the beagle dog to examine potential formulations of efavirenz/emtricitabine/tenofovir (see section “Pharmacokinetics”) limited tolerability information has

been generated for dogs that were dosed approximately weekly for up to 60 weeks. This study was not intended to serve as a safety study hence data is only considered supportive. However, once weekly dosing of the combination of efavirenz, emtricitabine and tenofovir DF at the doses used in this study was generally well tolerated for periods of up to 60 weeks with no overt toxicity. At the lower doses used in this study (150 mg of efavirenz, 50 mg of emtricitabine and 75 mg tenofovir DF), the exposure in dogs to emtricitabine and tenofovir was similar to that in patients while the exposure of efavirenz was ≥ 15-fold lower than that of human patients at steady-state.

Impurities and degradation products of the fixed combination product have been evaluated and have been toxicological qualified. There are no new impurities or degradation products for the fixed combination.

Ecotoxicity/environmental risk assessment

An environmental risk assessment has been performed according to the guideline on the applicable guideline (EMEA/CHMP/SWP/4447/00).

At phase I, the estimate values of predicted environmental concentrations ($PEC_{SURFACEWATER}$) were 0.0030 mg/L for efavirenz; 0.0010 mg/L for emtricitabine and 0.0012 mg/L for tenofovir disoproxil. As these values were above the action limit of 0.01 µg/L a phase II was required which comprises the following on-going programme:

- Chronic ecotoxicity and environmental fate studies with efavirenz, to be reported as follow-up measures.
- Studies with emtricitabine and tenofovir DF to investigate to determine PNEC values and PEC/NEC ratios, to be reported as follow-up measures.

An adsorption/desorption study for efavirenz showed that phase II tier B studies are not required. Efavirenz was found to have PEC/PNEC ratios with respect to surface water, ground water and microorganisms less than 1.

4. Clinical aspects

Introduction

The three active substances in the fixed combination of Atripla, i.e. efavirenz, emtricitabine and tenofovir DF, are already approved for combination antiretroviral therapy of HIV-1 infection (see details in section "Introduction" to the Scientific Discussion). Comprehensive clinical study programmes have been conducted for the individual compounds and the dual combination aimed at generating data on pharmacokinetics and pharmacodynamics, as well as establishing safety and efficacy. Therefore the development programme for Atripla focused on the generation of additional clinical data required to support the approval of this triple combination and comprised the following studies:

- five bioequivalence studies establishing the formulation for the fixed dose combination (GS-US-177-0101, GS-US-185R-0102, GS-US-177-0103, GS-US-177-0104, GS-US-177-0105). All these studies were identically designed; the details of the main bioequivalence study GS-US-177-0105 are summarised in Table 1;
- efficacy and safety data from three clinical studies investigating the combination of the three active substances either as free combination or as fixed combination in the final formulation (GS-01-934, GS-US-164-0107, AI266073); the study details are summarised in Table 2.

In the initial MAA dossier the bioequivalence study GS-US-177-0105 was identified as the primary data in support of the application. However, due to the concerns raised by the CHMP during the review of the application, the above-mentioned, additional efficacy and safety studies, in particular study AI266073, became of particular importance for the assessment.

The applicant did not seek scientific advice from the CHMP for this development. The Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection (CPMP/EWP/633/02) recognises the development of fixed dose combinations to reduce pill burden and states that the clinical data will depend on the nature of the combination. In particular a potentially new posology for the fixed dose combination and the level of documentation of the free combination would need to be considered to define the extent of clinical data needed. Due to the change of posology of one of the components, tenofovir DF (administered in fasting state instead of fed state), the CHMP confirmed the need to support the application with additional clinical efficacy data.

The initial application claimed the use of Atripla alone or in combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults; the approved indication limits its use for the treatment of human immunodeficiency virus-1 (HIV-1) infection in already virologically suppressed adults. The concomitant use with other antiretroviral agents is not supported by appropriate data. The recommended dose is one tablet taken orally once daily on an empty stomach and preferably at bedtime.

A paediatric development is not planned for this fixed combination medicinal product. Paediatric development programmes for the individual components including the dual combination have been or are being conducted. Due to the different dosing algorithm required for the individual compounds in the paediatric population the applicant claims that a fixed dose combination medicinal product is not suitable for this population.

Table 1 Summary of the design of the main bioequivalence study

Study Number	Study Objective(s)	Design	Treatments (Dose, Dosage Form)	Subjects Number (M/F) Type Age: Mean (range)
GS-US-177-0105	To evaluate the bioequivalence of a fixed-dose EFV/FTC/TDF tablet and EFV, FTC, and TDF administered concurrently as the individual components under fasted conditions	Randomized, open-label, single-centre, 2-treatment, 2-way crossover	**Reference:** single EFV tablet + single FTC capsule + single TDF tablet administered concurrently to fasted subjects **Test:** single fixed-dose combination tablet of EFV/FTC/TDF administered to fasted subjects Group 1: • Day 1 = test • Day 29 = reference Group 2: • Day 1 = reference • Day 29 = test	48 enrolled (13M/35F) Healthy subjects 30 (18-45) years

Table 2 Summary of the design of the main clinical efficacy and safety studies

Study Number	Study Objective(s)	Design	Study and Control Regimens	Number of Patients by Treatment
GS-01-934	To assess non-inferiority of EFV+FTC+TDF relative to EFV+ AZT/3TC in the treatment of HIV-1 infected antiretroviral naive patients	Randomized, open-label, parallel, multicenter, active controlled 144 weeks + 96 week extension	EFV+FTC+TDF to Week 96, then EFV+FTC/TDF vs EFV+ AZT/3TC From Week 144: EFV/FTC/TDF for all patients	511 patients treated: • EFV+FTC+TDF = 257 • EFV+AZT/3TC = 254
GS-US-164-0107 (COMET)	To characterize the risks, effectiveness, and benefits of switching from a AZT/3TC (twice daily)/efavirenz (once daily) regimen to an all-once daily regimen of TDF/FTC + efavirenz	Prospective, single-arm, open-label, uncontrolled, switch study 24 weeks	Switch from AZT/3TC (twice daily) + EFV (once daily) to FTC/TDF (200 mg/ 300 mg) tablet once daily + EFV (600 mg) once daily	402 patients treated
AI266073	To compare the efficacy and safety of the single tablet regimen EFV/FTC/TDF to unmodified HAART in HIV-1 infected subjects who have achieved stable virologic suppression for at least 3 months on their current HAART regimen	Randomized, open-label, parallel, multicenter, active controlled 48 weeks	EFV/FTC/TDF versus unchanged baseline regimen (ratio 2:1)	203 patients on EFV/FTC/TDF, 97 patients stayed on baseline regimen [SBR]

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

The pharmacokinetic properties of the individual components have been subject to comprehensive development programmes to support Marketing Authorisations either alone or in dual combinations. The pharmacokinetic development strategy for Atripla focused on the compatibility of the active ingredients with each other and with the other excipients of the formulation to demonstrate bioequivalence between this product and the concurrently administered individual dosage forms. Since adequate two-way interaction studies have been conducted for all three individual agents and, moreover, extensive clinical evidence of the use of these substances as free combination is available, the CHMP in principle considered it acceptable that new pharmacokinetic data was only provided to address bioavailability aspects.

The following provides a summary of the already available pharmacokinetic data on the individual active substances as well as details of the additional clinical studies specific for Atripla.

- Absorption

  - ***Efavirenz:*** Peak efavirenz plasma concentrations of 1.6 - 9.1 µM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days. In 35 patients receiving

efavirenz 600 mg once daily, steady state C_{max} was 12.9 ± 3.7 µM (29%) [mean ± S.D. (% C.V.)], steady state C_{min} was 5.6 ± 3.2 µM (57%), and AUC was 184 ± 73 µM·h (40%).

- ***Emtricitabine:*** Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. In 20 HIV infected patients receiving 200 mg emtricitabine daily as hard capsules, steady-state plasma emtricitabine peak concentrations (C_{max}), trough concentrations (C_{min}) and area under the plasma concentration time curve over a 24-hour dosing interval (AUC) were 1.8±0.7 µg/ml, 0.09±0.07 µg/ml and 10.0±3.1 µg·h/ml, respectively. Steady-state trough plasma concentrations reached levels approximately 4-fold above the *in vitro* IC_{90} values for anti-HIV activity.
- ***Tenofovir DF:*** Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%.

Bioequivalence

Reports of the five bioequivalence studies have been submitted. Studies GS-US-177-0101, GS-US-185R-0102 and GS-US-177-0103 failed to show bioequivalence between the fixed dose triple combination product Atripla as compared to the concurrently administered individual medicinal products containing efavirenz, emtricitabine and tenofovir DF, and led to further pharmaceutical development to identify the appropriate formulation composition. Studies GS-US-177-0104 and GS-US-177-0105 demonstrated bioequivalence between the formulations tested and the individual dosage forms of efavirenz, emtricitabine and tenofovir DF; study GS-US-177-0105 used the intended commercial formulation of Atripla.

Study no. GS-US-177-0105

STUDY DESIGN

This was a randomized, single-dose, open-label, two-way crossover, Phase 1 study to assess the bioequivalence of a fixed-dose triple-combination tablet of efavirenz, emtricitabine, and tenofovir DF (EFV/FTC/TDF, test treatment) compared with concurrent administration of individual dosage forms of efavirenz, emtricitabine, and tenofovir DF (EFV+FTC+TDF, reference treatment) to healthy adults under fasting conditions. The crossover study consisted of two periods, Period 1 (Day 1 to 28) and Period 2 (Day 29 to 50). Subjects were considered to have completed a period if they completed the last day of pharmacokinetic sampling within that period (i.e. Day 22 or 50). Subjects were screened for eligibility to participate in the study within 30 days before randomisation.

TEST AND REFERENCE PRODUCTS

Atripla (600 mg efavirenz, 200 mg emtricitabine, 300 mg tenofovir DF) in the intended commercial formulation was used as the test product. The reference products were commercially available formulation of Sustiva (600 mg efavirenz), Emtriva (200 mg emtricitabine) and Viread (300 mg tenofovir DF), all from the United States of America. The identity of these commercial formulations with the medicinal products approved in the EU/EEA has been confirmed by the applicant.

POPULATION(S) STUDIED

Healthy subjects were investigated in this study to remove the confounding effects of background antiretroviral and other therapies and to avoid the need to make multiple, short-term changes in treatment regimens of HIV-infected patients for the purpose of examining pharmacokinetic (PK) parameters. The planned enrolment was 48 subjects to obtain data from 38 subjects available for pharmacokinetics evaluation. 73% of the participants in the study were female, and 90% were of hispanic origin.

ANALYTICAL METHODS

Plasma samples were analysed using LC/MS/MS. Two bioanalytical methods were employed for the active pharmaceutical ingredients, one of which was used for the determination of emtricitabine and tenofovir and the other one for efavirenz. Validations have been performed according to current standards, and clinical compliance audit certificates were provided.

PHARMACOKINETIC VARIABLES

The primary pharmacokinetic parameters for assessing bioequivalence between the fixed dose triple-combination tablet and the individual dosage forms administered concurrently were $AUC_{0\text{-last}}$, AUC_{inf}, and C_{max}. Pharmacokinetic parameters were estimated by application of a non-linear model using standard noncompartmental methods. The linear/log trapezoidal rule was used in conjunction with the appropriate noncompartmental model, with input values for dose, time of dose, plasma concentrations, and corresponding real time values based on drug dosing times.

STATISTICAL METHODS

The comparison of the pharmacokinetic values between the test and reference treatments was made by analysis of variance (ANOVA). Bioequivalence was concluded if the 90% confidence interval for the ratio of geometric means (test / reference) fell within 80% to 125% for the primary pharmacokinetic parameters, C_{max}, $AUC_{0\text{-last}}$, and AUC_{inf} for each analyte.

RESULTS

The results of the pharmacokinetic evaluation are presented in Table 3.

These data demonstrate bioequivalence of Atripla with the respective co-administered individual products. It was noted though that the resulting pharmacokinetic data of efavirenz differs considerably from historical data with regard to the half life; additional analyses requested by the CHMP indicated that this effect is mainly due to differences in the study populations (gender and ethnicity) with a considerable proportion of females and non-Caucasians known to have a prolonged half life. Special consideration was given to the fact that the study was conducted under fasting conditions, which is not in accordance with the posology of the currently approved SmPC of tenofovir-containing products in the EU/EEA.

Table 3 Pharmacokinetic results of study GS-US-177-0105

	Efavirenz (N = 38)			Emtricitabine (N = 41)			Tenofovir (N = 41)		
Para-meters	**Test (%CV)**	**Reference (%CV)**	**GMR (%) (90% CI)**	**Test (%CV)**	**Reference (%CV)**	**GMR (%) (90% CI)**	**Test (%CV)**	**Reference (%CV)**	**GMR (%) (90% CI)**
C_{max} (ng/ml)	2276.4 (26.7%)	2283.5 (30.6)	99.98 (93.37, 106.88	2130.6 (25.3)	2384.4 (20.4)	88.84 (84.02, 93.94)	325.1 (34.2)	352.9 (29.6)	91.46 (84.64, 98.83)
$AUC_{0\text{-last}}$ (ng·hr/ml)	125,041 (25.9)	132,784 (27.3)	95.73 (90.5, 101.26)	10,683 (18.1)	10,874 (14.9)	97.98 (94.90, 101.16)	1948.8 (32.9)	1969.0 (32.8)	99.29 (91.02, 108.32)
AUC_{inf} (ng·hr/ml)	143,602 (32.0)	155,310 (35.1)	88.92, 101.91)	10,855 (17.9)	11,054 (14.9)	97.96 (94.86, 101.16)	2314.0 (29.2)	2319.4 (30.3)	100.45 (93.22, 108.23)
T_{max} (h) median	3.5	3.75	-	48.2	48.2	-	1.00	0.75	-
$T_{1/2}$ (h), median	164.4 (58.8, 532.6)	166.1 (43.0, 381.2)	-	10.6 (5.9, 47.5)	11.4 (6.6, 38.1)	-	18.5	17.2	-

Influence of food

Administration of ***efavirenz*** tablets with a high-fat meal increased the mean AUC and C_{max}, of efavirenz by 28% and 79%, respectively, compared with administration in the fasted state (Study DMP266-110). The approved SmPCs for the respective medicinal products (Sustiva, Stocrin) recommend administration of efavirenz on an empty stomach, preferably at bedtime, because the increased exposure to efavirenz when administered with food may lead to an increase in the frequency and severity of adverse events.

Compared with fasted administration, dosing of a fixed-dose combination of ***tenofovir*** DF and emtricitabine with either a high-fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35% and 15%, respectively, with no effect on ***emtricitabine*** exposure (Study GS-US-104-172). The lack of a food effect with emtricitabine in this study is consistent with the results of the previous food effect study with the single agent (Study FTC-111) and the approved SmPC for Emtriva which indicates that emtricitabine may be taken with or without food.

The increased exposure to ***tenofovir*** when administered with food is consistent with findings from previous food effect studies of the single agent (Studies GS-00-914 and GS-00-903). As a consequence the approved SmPCs for the respective medicinal products (Viread, Truvada) recommend administration of tenofovir DF with food.

No studies on the influence of food have been conducted with the fixed triple combination tablet Atripla. Additional data to support the applicant's claim that tenofovir DF may be administered with or without food was provided. This included a historical comparison of two steady-state interaction studies (GS-01-932 [light meal] and GS-00-909 [fasted]), resulting in a comparable bioavailability of tenofovir irrespective of food intake. However, necessary data for the assessment of the relevance of this comparison were missing. Moreover, the CHMP considered that data from other studies (e.g. GS-US-104-172 and GS-00-914) provided conflicting results thus questioning the validity of the applicant's approach. In addition it was claimed that a possible decrease in plasma exposure due to the effect of intake without food on tenofovir DF would not be of clinical relevance, as the active moiety, tenofovir diphosphate, acts intracellularly and exhibits a protracted half-life, however no substantiating pharmacokinetic data was submitted. Reference was also made to the efficacy data from study GS-01-934 showing no difference in virologic response between patients taking their medication with or without food; this data is presented in the section "Clinical efficacy".

- Distribution

  - ***Efavirenz:*** Efavirenz is highly bound to human plasma proteins (approximately 99.5 - 99.75%), predominantly to albumin. In HIV-1 infected patients (n = 9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.
  - ***Emtricitabine:*** *In vitro* binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 µg/ml. The mean plasma to blood concentration ratio was approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0. The apparent volume of distribution after intravenous administration of emtricitabine was 1.4±0.3 l/kg, indicating that emtricitabine is widely distributed throughout the body to both intracellular and extracellular fluid spaces.
  - ***Tenofovir:*** Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

- Metabolism

  - ***Efavirenz:*** Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In *in vitro* studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism.
  - ***Emtricitabine:*** There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). Emtricitabine did not inhibit *in vitro* drug metabolism mediated by the following human CYP450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.
  - ***Tenofovir:*** Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate

- Excretion

  - ***Efavirenz:*** Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40 - 55 hours after multiple doses (see also results of study GS-US-155-0105). Approximately 14 - 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.
  - ***Emtricitabine:*** Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 ml/min (4.03 ml/min/kg). Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.
  - ***Tenofovir:*** Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Dose proportionality and time dependencies

  - ***Efavirenz:*** Dose related increases in C_{max} and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. In HIV infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were linear with daily doses of 200 mg, 400 mg, and 600 mg. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. In uninfected volunteers, multiple doses of 200 - 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 - 42% lower) and a shorter terminal half-life as compared to single dose half-life.

- ***Emtricitabine:*** The pharmacokinetics of emtricitabine are proportional to dose over the dose range of 25-200 mg following single or repeated administration. No time dependency has been described for emtricitabine.
- ***Tenofovir:*** The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range of 75 to 600 mg and were not affected by repeated dosing at any dose level. No time dependency has been described for tenofovir.

- Special populations

Impaired renal function

- ***Efavirenz:*** The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.
- ***Tenofovir and Emtricitabine:*** Two studies in non-HIV-1 infected subjects determined the pharmacokinetics of tenofovir (Study GS-01-919) and emtricitabine (Study FTC-107) in the presence of varying degrees of renal impairment, including end-stage renal disease (ESRD) requiring haemodialysis. The pharmacokinetic data for both tenofovir and emtricitabine indicate that dose interval adjustment is necessary for subjects with moderate or severe renal impairment (CL_{cr} < 50 ml/min) and those with ESRD requiring haemodialysis. In subjects with mild renal impairment, the pharmacokinetics of tenofovir and emtricitabine are not substantially altered to warrant dose adjustment.

The fixed-dose combination of efavirenz, emtricitabine and tenofovir DF cannot be recommended for patients with moderate or severe renal impairment (CL_{cr} < 50 ml/min) because these patients require dose interval adjustment of emtricitabine and tenofovir DF, which cannot be achieved with this fixed-dose combination tablet. Increasing the dosing interval for renally impaired patients, as instructed in the approved SmPCs for Viread, Emtriva and Truvada, would reduce exposure to efavirenz because its elimination is not affected by renal impairment.

Impaired hepatic function

- ***Efavirenz:*** The pharmacokinetics have not been adequately studied in patients with hepatic impairment. In the single patient studied with severe hepatic impairment (Child Pugh Grade C, Study AI266033), half-life was doubled indicating a potential for a much greater degree of accumulation.
- ***Emtricitabine:*** Emtricitabine is not significantly metabolized by liver enzymes (< 13% of oral dose, Study FTC-106); therefore, the impact of liver impairment on the pharmacokinetics of emtricitabine should be limited for this agent. The pharmacokinetics of emtricitabine have not been studied in hepatically impaired subjects. In patients infected with HBV, the pharmacokinetics of emtricitabine was similar to those determined previously in other populations, i.e., HIV-1 infected patients and healthy volunteers (FTCB-101). In addition, the safety profile of emtricitabine in a Phase 3 HBV trial (FTCB-301) was similar to the placebo arm of the study
- ***Tenofovir:*** The pharmacokinetics of tenofovir after a 300-mg dose of tenofovir DF were studied in non-HIV-1 infected patients with varying degrees of hepatic impairment, according to CPT classification (Study GS-01-931 A/B). Tenofovir pharmacokinetics were not substantially altered in patients with hepatic impairment compared with unimpaired patients, suggesting that no dose adjustment of tenofovir DF is required in these subjects.

Because efavirenz undergoes extensive cytochrome P450–mediated metabolism and because there is limited clinical experience in patients with hepatic impairment, the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF must not be administered to patients with severe hepatic impairment (CPT Grade C).

Gender

The pharmacokinetics of efavirenz, emtricitabine, and tenofovir DF are similar in male and female patients. Although limited data suggest that females as well as Asian and Pacific Island patients may have higher exposure to efavirenz, they do not appear to be less tolerant of efavirenz.

Clinically relevant differences in the pharmacokinetics of the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF with respect to demographic variables are not anticipated based on data available for the individual agents.

Elderly

The pharmacokinetics of efavirenz, emtricitabine, or tenofovir have not been evaluated in patients > 65 years old.

The fixed-dose combination of efavirenz, emtricitabine and tenofovir DF should be administered with caution to elderly patients, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this subpopulation.

Children

The fixed-dose combination of efavirenz, emtricitabine and tenofovir DF is not recommended for use in children and adolescents (< 18 years). The pharmacokinetics, safety and efficacy of efavirenz and emtricitabine have been investigated in HIV-1 infected children; however, efavirenz has not been studied in pediatric patients who are less than 3 years old or weigh less than 13 kg. In general, the pharmacokinetics of efavirenz and emtricitabine in pediatric patients are similar to those seen in adults. Only preliminary data are available on the pharmacokinetics of tenofovir in pediatric patients and its safety and effectiveness in this population have not been established.

- Pharmacokinetic interaction studies

In vitro

- ***Efavirenz*** has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4. Coadministration of efavirenz with drugs primarily metabolized by CYP2C9, CYP2C19, and CYP3A4 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs that induce CYP3A4 activity would be expected to increase the clearance of efavirenz, resulting in lowered plasma concentrations.
- Both ***emtricitabine*** and ***tenofovir DF*** are considered to have a low potential for CYP450 mediated interactions based on the results of *in vitro* experiments and the known renal elimination pathways of both agents. Since both agents are primarily renally excreted, there is potential for interaction with other drugs that are similarly eliminated. Drugs that decrease renal function may also increase serum concentrations of emtricitabine and tenofovir.

Concomitant use of the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF together with nephrotoxic agents must be avoided.

In vivo

No specific pharmacokinetic interaction studies have been performed with the fixed combination product, and the information described in the SmPC is based on extrapolation from data conducted with the individual agents. This was considered acceptable by the CHMP due to the extensive clinical evidence of the use of these active substances as free combinations. The following is a summary of the information most relevant to this combination.

Because efavirenz has been shown in vitro to induce CYP3A4, and to inhibit CYP2C9, CYP2C19, and CYP3A4 isozymes, the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids because inhibition of their metabolism may lead to serious, life-threatening adverse events. The fixed-dose combination of efavirenz, emtricitabine and tenofovir DF must not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations, and voriconazole increases efavirenz exposure.

Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort (Hypericum perforatum). This is due to induction of drug metabolizing enzymes and/or transport proteins by St. John's wort. Herbal preparations containing St. John's wort must not be used concomitantly with the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF. Special precautions should be followed for stopping St. John's wort when initiating treatment with efavirenz.

The effects of efavirenz on the pharmacokinetics of clarithromycin, methadone, ethinyl estradiol, rifabutin, and sertraline have been established. The SmPC for the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF provides appropriate guidance for the management of patients administered these concomitant medications in conjunction with the combination tablet. Since rifampicin reduced efavirenz AUC and C_{max} by 26% and 20% when coadministered, an additional 200 mg/day of efavirenz is recommended when rifampicin is administered with the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF.

Drug interactions have also been established between efavirenz and the PIs, ritonavir, atazanavir, lopinavir/ritonavir, saquinavir, indinavir, and amprenavir and are adequately described in the SmPC. Additionally, coadministration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin, pravastatin, or simvastatin has been shown to substantially reduce the plasma concentration of the statins in uninfected volunteers. Cholesterol levels should be periodically monitored. Dosage adjustments of statins may be required when coadministered with the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF.

Similarly dose adjustment of the calcium channel blocker, diltiazem, should be considered based on clinical response when administered with the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF due to decreased plasma levels of diltiazem when coadministered with efavirenz. Although the pharmacokinetics of efavirenz were slightly increased (11% to 16%) when coadministered with diltiazem, these changes are not considered clinically significant.

No dose recommendation can be made for the use of the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF with carbamazepine because of a two-way interaction resulting in decreased concentrations of both efavirenz and carbamazepine. Carbamazepine levels should be periodically monitored. An alternative anticonvulsant treatment should be considered.

Coadministration of tenofovir DF with efavirenz did not influence plasma efavirenz concentrations. Furthermore, administration of efavirenz with tenofovir DF had no effect on plasma concentrations of tenofovir.

No clinically relevant drug interaction studies have been identified between emtricitabine and the coadministered drugs investigated (i.e., indinavir, famciclovir, stavudine, zidovudine, and tenofovir DF).

Interactions between tenofovir DF and other antiretroviral drugs were observed for didanosine (exposure increase) and atazanavir (without ritonavir, exposure decrease). No clinically relevant pharmacokinetic interactions were observed for abacavir, adefovir dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, nelfinavir, or saquinavir/ritonavir. After multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant drug interactions between these agents and tenofovir DF.

Interactions between PIs and efavirenz and tenofovir DF require guidance for concomitant use with the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF.

The fixed-dose combination of efavirenz, emtricitabine and tenofovir DF should not be coadministered with related drugs that contain the same active components (i.e., efavirenz, emtricitabine, or tenofovir DF). Because of similarities with emtricitabine, the fixed-dose combination of efavirenz, emtricitabine and tenofovir DF should not be coadministered with other cytidine analogues, such as lamivudine

All relevant information on pharmacokinetic interactions is adequately reflected in the SmPC.

Pharmacodynamics

Comprehensive programmes investigating the intracellular metabolism, mechanism of action, and *in vitro* activity of efavirenz, emtricitabine, and tenofovir have been conducted and the data has been assessed. No further supportive clinical pharmacology studies were considered warranted by the CHMP on the basis of available clinical pharmacology data and the sufficiently documented clinical experience with the use of efavirenz, emtricitabine and tenofovir DF, both alone and in combination, for the treatment of HIV-1 infection. The following summarises the available evidence with regard to pharmacodynamic data:

- Mechanism of action

Efavirenz is a non-nucleoside reverse transcriptase inhibitor of HIV-1 (NNRTI) and thus acts via non-competitive inhibition of the HIV reverse transcriptase. Emtricitabine is a nucleoside analogue of cytidine (NRTI) and tenofovir is a nucleotide analogue of adenosine (NtRTI); both function as competitive inhibitors of the HIV reverse transcriptase.

- Primary and Secondary pharmacology

In vitro studies have demonstrated potent antiviral activity of efavirenz, emtricitabine, and tenofovir DF against laboratory and clinical strains of HIV-1. The findings of *in vitro* pharmacodynamic investigations suggest a low potential for intracellular drug antagonism between tenofovir or emtricitabine and other antiretroviral compounds. The dual combination of tenofovir and emtricitabine showed additive anti-HIV-1 activity in PBMCs and synergistic anti-HIV-1 activity in the leukemic MT-2 cell line. The additive-to-synergistic anti-HIV-1 activity observed with two drug combinations of efavirenz, emtricitabine, and tenofovir in multiple *in vitro* assay systems supports the use of these agents in combination in HIV-1 infected patients. Furthermore, the antiviral effects and cytotoxicity of efavirenz when paired individually with 12 other marketed antiretrovirals and the anti-HBV drug adefovir against HIV-1 in MT-2 cells was investigated (see section "Non-clinical aspects / Pharmacodynamic drug interactions"). The relevant data from this body of evidence is adequately described in the SmPC.

<u>Resistance</u>

The single substitutions which led to the highest resistance to efavirenz in cell culture were L100I (17 to 22-fold resistance) and K103N (18 to 33-fold resistance). K103N was also the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in 90% of patients receiving efavirenz with virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medications used in combination with efavirenz. However, cross resistance with other NNRTIs is extensive

Resistance has been seen *in vitro* and in some HIV-1 infected patients due to the development of the M184V/I mutation with emtricitabine and the K65R mutation with tenofovir. No other pathways of resistance to emtricitabine or tenofovir have been identified. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to tenofovir. The K65R mutation can also be selected for by abacavir, didanosine or zalcitabine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in patients with HIV-1 harbouring the K65R mutation.

Resistance data generated in study GS-01-934 through 144 weeks were in agreement with previous results. The proportion of patients who developed any resistance in the AZT/3TC group by Week 96 (20/243, 8%) was double that observed in the emtricitabine + tenofovir DF group (10/244, 4%); however, the difference was not statistically significant ($p = 0.06$). Resistance to efavirenz was the most common form of resistance that developed with the K103N mutation being the most common mutation. Noteworthy, no patient in the emtricitabine + tenofovir DF group developed the K65R mutation selected by tenofovir DF.

Clinical efficacy

The clinical efficacy data of Atripla is focussed on the one hand on the demonstration of an overall positive benefit risk ratio of the triple combination and on the other hand on demonstrating that intake of tenofovir DF in the fasting state (deviating from the currently approved recommendation) does not impair the clinical efficacy of the drug.

- Dose response studies

Comprehensive data on dose response studies with efavirenz, emtricitabine or tenofovir can be summarised as follows:

- ***Efavirenz:*** Initially, the dose of 200 mg was selected based on preclinical and clinical pharmacokinetic data obtained from the early studies. Considering the long half life of 40-55 hours, once daily dosing regimen was considered possible. Since efavirenz administered at the dose of 200 mg has shown a good tolerability, doses of 400 mg and 600 mg were evaluated in terms of efficacy and safety. The 600 mg dose proved superior in terms of maintained suppression of HIV-RNA levels below the limit of quantification; the rate of CNS adverse events was increased but still considered to be at a tolerable level. Based on this data the 600 mg dose was selected for further clinical development.
- ***Emtricitabine:*** In a dose escalation study to investigate the safety, pharmacokinetics and antiviral activity of multiple repeated doses median changes in HIV-1 RNA from baseline to Day 15 increased with the dose and reached an apparent plateau at doses between 200 mg qd and 200 mg bid. In a monotherapy study comparing emtricitabine (at 25 mg, 100 mg and 200 mg q.d.) with lamivudine monotherapy (at 150 mg b.i.d.) over 10 days, a dose response relationship was observed for viral suppression as analysed by AAUCMB through Day 12. There was a statistically significant difference between the emtricitabine 200 mg q.d. and the lamivudine groups with respect to AAUCMB through Days 11 and 12. These results, along with the pharmacokinetic data and anti-viral activity of emtricitabine, supported the choice of 200 mg once daily as the recommended dose.
- ***Tenofovir:*** Dose-proportional pharmacokinetics of tenofovir following oral administration were observed and the long terminal half life supported a once daily dosage regimen. The dose of 245 mg daily was supported by a significant viral load decrease compared to placebo with an acceptable safety profile.

- Main studies

Study data on the triple combination efavirenz, emtricitabine or tenofovir DF from studies GS-01-934 (week-144 and week-168 reports), study GS-US-164-0107 (week-24 report) and study AI266073 (week-24 interim report) is summarized in the following paragraphs:

Study GS-01-934

METHODS

Open-label, parallel, multicenter, active-controlled study with 1:1 randomization; patients were stratified on the basis of screening CD4+ cell count (< or ≥ 200 cells/mm3); emtricitabine and tenofovir DF are dosed as the emtricitabine/tenofovir DF fixed-dose combination tablet during weeks 96 through 144. After completing 144 weeks of treatment with study drug, patients from both study arms were given the option to roll over into a 96-week protocol extension and switch their treatment regimen to a fixed-dose, triple-combination formulation of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir DF 300 mg. Total duration of the study is 240 weeks.

Study Participants

Antiretroviral-naive, HIV-1 infected patients with plasma HIV-1 RNA concentrations > 10,000 copies/ml and any CD4+ cell count.

Treatments

Test product, dose, and mode of administration:

- Efavirenz 600 mg once daily, orally, without regard to meals,
- Emtricitabine 200 mg once daily, orally, without regard to meals, and
- Tenofovir DF 300 mg once daily, orally, without regard to meals.

Nevirapine 200 mg twice daily orally (according to the nevirapine prescribing information) could replace efavirenz in the event of efavirenz-associated central nervous system (CNS) toxicity.

Reference therapy, dose, and mode of administration:

- Efavirenz 600 mg once daily, orally, without regard to meals and
- Lamivudine/zidovudine (Combivir) 150 mg/300 mg twice daily, orally, without regard to meals.

Nevirapine 200 mg twice daily orally (according to the nevirapine prescribing information) could replace efavirenz in the event of efavirenz-associated CNS toxicity.

Objectives

The primary objective was to assess noninferiority of emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) in combination with efavirenz relative to lamivudine/zidovudine (Combivir) in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive patients, determined by the achievement and maintenance of confirmed HIV-1 RNA < 400 copies/ml through Week 48, as defined by the time-to-loss-of-virologic-response (TLOVR) algorithm.

Secondary objectives were to evaluate the safety and tolerability and to assess non-inferiority of emtricitabine and tenofovir DF in combination with efavirenz relative to lamivudine/zidovudine in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive patients.

Outcomes/endpoints

Efficacy**:** The primary efficacy endpoint was the achievement and maintenance of confirmed HIV-1 RNA concentrations < 400 copies/ml through Week 48, as defined by the TLOVR algorithm. The modified intent-to-treat (MITT) analysis set, which excluded patients with baseline nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance, was used in this analysis.

The secondary efficacy endpoints included the achievement and maintenance of confirmed HIV-1 RNA concentrations < 50 copies/ml through Week 48 and the achievement and maintenance of confirmed HIV-1 RNA concentrations < 400 copies/ml and < 50 copies/ml through Week 96 and through Week 144, as defined by the TLOVR algorithm. In addition to excluding patients with

baseline NNRTI resistance (MITT), the Week 96 efficacy analysis set excluded Week 48 TLOVR responders who did not consent to continue the study after Week 48. Further evaluations:

- genotypic and phenotypic resistance,
- effect of dosing emtricitabine and tenofovir DF without regard to meals.

Safety: Adverse events, clinical laboratory tests.

Sample size

A total of 517 patients were randomized, 258 patients to the emtricitabine + tenofovir DF group and 259 patients to the lamivudine/zidovudine group.

Statistical methods

The primary safety and efficacy analysis was conducted upon completion of 48 weeks on study by the last enrolled patient. This interim synopsis report presents results of safety and efficacy analyses conducted after the last enrolled patient completed 96 weeks on study. The Week 144 analysis of efficacy and safety was conducted after the last patient completed 144 weeks on study, and the Week 240 analysis of efficacy and safety will be conducted after the last patient completes 240 weeks on study.

Efficacy: The non-inferiority of emtricitabine and tenofovir DF in combination with efavirenz relative to lamivudine/zidovudine in combination with efavirenz through 144 weeks was assessed using a two-sided 95% confidence interval for the baseline CD4+ cell count stratum-weighted difference in the proportions of patients who achieved and maintained confirmed HIV-1 RNA < 400 copies/ml and < 50 copies/ml at Week 144 (emtricitabine + tenofovir DF group minus lamivudine/zidovudine group). The emtricitabine + tenofovir DF group was declared noninferior to the lamivudine/zidovudine group if the lower confidence bound was ≥ −0.13. Randomisation was stratified according to baseline CD4 cell count (<200 / ≥200 cells/ml) and HIV RNA (<100,000 / ≥100,000 copies/ml).

RESULTS

Participant flow

By week 48, 487 patients were available for the MITT analysis (of the initially randomised 517 patients). By week 144, 161 (63%) patients in the emtricitabine + tenofovir DF group and 126 (50%) lamivudine/zidovudine group remained on study. The most common reasons for premature discontinuation were 'patient lost to follow up' and 'subject withdrew consent'. More patients in the lamivudine/zidovudine group withdrew for adverse events (11% vs. 5%). Between week 144 and week 168, nine patients discontinued the study regimen, mostly for withdrawal of consent (n = 6), and one each for adverse event, death (cardiac arrest due to cardiac dysfunction NOS, (considered not related to Atripla) and subject lost to follow-up).

Conduct of the study

The study was started with administration of all three active substances as separate medicinal products. From week 96 to 144, emtricitabine and tenofovir DF were administered as dual fixed combination. Through 144 weeks study drugs (FTC and TDF) were administered without regard to food. After completing 144 weeks of treatment with study drug, patients from both treatment groups were given the option to roll over into a protocol extension and switch their treatment regimen to Atripla, dosed on an empty stomach, preferably at bedtime.

Baseline data

Demographics as well as baseline disease characteristics appear well balanced between the two treatment groups with the majority of patients being white males. Noteworthy, 40% of this ART naïve treatment population present with an advanced disease stage, i.e. AIDS.

Outcomes and estimation

At week 48 superiority of the FTC/TDF regimen with respect to the primary variable was shown.

In the secondary efficacy analyses at week 144 (efficacy analysis set, N = 456 for HIV-1 RNA ≤400 copies/mL), a significantly higher proportion of patients in the emtricitabine + tenofovir DF group compared with the lamivudine/zidovudine group achieved and maintained confirmed HIV-1 RNA ≤400 copies/mL through Week 144, as defined by the TLOVR algorithm. The difference in proportions, weighted by baseline CD4+ cell count stratum, between the emtricitabine + tenofovir DF group and the lamivudine/zidovudine group was 13%, and the 95% confidence interval (CI) was 4% to 22%. The proportion of patients who achieved and maintained plasma HIV-1 RNA < 50 copies/mL was similar between the treatment groups and met the pre-specified criteria for non-inferiority.

Through 144 weeks of this study, in which study drugs (FTC and TDF) were administered without regard to food, treatment response rates among patients who responded to a dosing questionnaire (N=164/227 in FTC/TDF-group) were numerically slightly different between those who reported routinely dosing the regimen of efavirenz, emtricitabine, and tenofovir DF with food, and those who reported routinely dosing without food, i.e., at least 1 hour before or after a meal (see Table 4).

Table 4 Effect of dosing with or without food on treatment outcomes at week 144

	EFV + FTC + TDF		EFV + AZT/3TC	
Responses to Dosing Questionnaire, n/N (%)	164/227	(72%)	130/231	(56%)
Took Drugs With Food (within < 1 hour)	40/164	(25%)	47/130	(36%)
Took Drugs Without Food (within ≥ 1 hour)	124/164	(75%)	47/130	(36%)
Both[a]	NA		49/130	(38%)
Responder at Week 144, n/N (%)				
HIV-1 RNA < 400 copies/ml				
With Food	39/40	(98%)	43/47	(91%)
Without Food	117/124	(94%)	42/47	(89%)
Both[a]	NA		45/49	(92%)
HIV-1 RNA < 50 copies/ml				
With Food	36/40	(90%)	43/47	(91%)
Without Food	107/124	(86%)	41/47	(87%)
Both[a]	NA		43/49	(88%)

NA, not applicable

a Routinely took one daily dose of AZT/3TC with food and one daily dose of AZT/3TC without food

The duration of Study GS-01-934 was further extended from 144 to 240 weeks. An analysis was performed 24 weeks after initiation of Atripla (Week 168); the efficacy data is presented in Table 5.

Table 5 Proportion of Responders at Atripla Baseline and After 24 Weeks of Atripla Treatment in Study GS-01-934 (ITT, Missing = Failure)

	Original Study Treatment Group		All Atripla
	EFV + FTC + TDF (N = 160)	EFV + AZT/3TC (N = 126)	(N = 286)
Subjects with HIV-1 RNA < 400 copies/mL, n (%)			
Atripla Baseline (Week 144)	158 (99%)	125 (99%)	283 (99%)
Atripla Week 24 (Week 168)	157 (98%)	121 (96%)	278 (97%)
p-value[a]	0.65	0.10	0.13
Subjects with HIV-1 RNA < 50 copies/mL, n (%)			
Atripla Baseline (Week 144)	151 (94%)	122 (97%)	273 (95%)
Atripla Week 12 (Week 156)	143 (89%)	117 (93%)	260 (91%)
p-value[a]	0.78	1.0	**0.02**

[a] p-values are calculated using McNemar test

The statistically significant difference in subjects with HIV-1 RNA < 50 copies/ml may be driven by 8 subjects with missing data, all of whom had HIV-1 RNA concentration < 50 copies/ml at their last available measurement. Nevertheless, this statistically significant difference, especially together with a statistically significant decrease in CD4-cell counts between weeks 144 and 168 (overall median of -14 cells; p=0.03), is noteworthy.

Study GS-US-164-0107 (COMET Study)

METHODS

A prospective, single-arm, open-label switch study in treatment-experienced HIV-1 infected, virologically suppressed patients on a stable regimen of efavirenz taken with lamivudine/zidovudine, who had evidence of adverse clinical or laboratory effects associated with lamivudine/zidovudine or who might benefit from a simplified, once-daily antiretroviral regimen, regardless of lamivudine/zidovudine tolerability status.

Study Participants

HIV-1 infected, virologically suppressed patients on a stable regimen of efavirenz taken with lamivudine/zidovudine (> 18 years, on a stable regimen consisting of EFV (QD) and lamivudine/zidovudine (BID) for ≥ 8 weeks)

Treatments

Subjects were instructed to take one tablet of emtricitabine/tenofovir DF and one tablet of efavirenz, at the same time, once daily, without regard to meals.

Objectives

The objective of this study was to characterize the risks, effectiveness, and benefits of switching from a lamivudine/zidovudine (Combivir, twice daily) + efavirenz (once daily) regimen to an all once-daily regimen of emtricitabine/tenofovir DF (Truvada) + efavirenz.

Outcomes/endpoints

Efficacy: Overall response to treatment was assessed as the proportion of subjects with HIV-RNA<400 copies/ml at week 24.

Safety: Assessment of clinical adverse events and laboratory tests.

Sample size

The planned enrolment was 400 patients. Statistical power calculation was not considered for sample size determination. The sample size was based on the feasibility of conducting such a trial.

Statistical methods

Descriptive statistics were used to summarize the observed results and changes from baseline for each of the endpoints. Appropriate tests of significance, paired-tests for assessing observed changes from baseline were used to assess the statistical significance.

RESULTS

Participant flow

A total number of 411 patients were enrolled, of which 372 completed the study.

Baseline data

The majority of participants were male (83%), White (76%), and switched because they "might benefit from simplified regimen" (84%). Mean prior antiretroviral therapy was 4.9 years with a mean of 4 years on lamivudine/zidovudine.

Numbers analysed

- Evaluable for efficacy: 401 patients
- Evaluable for safety: 402 patients

Outcomes and estimation

The efficacy data at week 24 is presented in Tables 6 and 7. The Modified Intent-to-Treat (MITT) analysis is displayed; this set excludes subjects who had a major eligibility violation (HIV-1 RNA ≥ 1000 copies/ml at screening or baseline). A window of 5 days after the last dose of study drug was also considered for summarization and analysis of efficacy and questionnaire data.

Table 6 HIV–1 RNA < 400 copies/ml at week 24 (MITT Analysis Set)

	MITT Analysis Set (N = 401)	
HIV-1 RNA < 400 copies/mL, n (%)	**Missing = Excluded**	**Missing = Failure**
Baseline	400/401 (99.8%)	400/401 (99.8%)
Week 24	340/384 (89%)	340/401 (85%)

Table 7 HIV–1 RNA < 50 copies/ml at week 24 (MITT Analysis Set)

	MITT Analysis Set (N = 401)	
HIV-1 RNA < 50 copies/mL, n (%)	**Missing = Excluded**	**Missing = Failure**
Baseline	258/401 (64%)	258/401 (64%)
Week 24	274/355 (77%)	274/384 (71%)
p-value[a]	<0.001	0.021

[a] p-values are calculated using McNemar test

Ancillary analyses

A total of 348 subjects (87%) had ≥ 95% adherence with study drug. Of those, mean emtricitabine/tenofovir DF treatment adherence calculated by pill count was 98%. By questionnaire, (answered by 318 patients for weekly recall, and 322 for monthly recall), 86% of subjects reported taking study drugs for the previous week and month before the visit.

Study AI266073

METHODS

An ongoing, Phase 4, randomized, open-label, clinical study comparing the single tablet regimen Atripla to unmodified HAART in HIV-1 infected patients who have achieved stable virologic suppression (< 200 copies/ml on two consecutive measurements) for at least 3 months on their current HAART regimen.

Study Participants

Patients must be on their first HAART regimen or have documented viral suppression on a previous PI-based regimen at the time of prior change in therapy. HAART must consist of either a PI (with or without ritonavir) + at least 2 NRTIs (alternatively 1 NRTI/1 NtRTI) or an NNRTI + at least 2 NRTIs (alternatively 1 NRTI/1 NtRTI). Patients on a HAART-regimen containing TDF, FTC and EFV and patients who have known resistance to any of the study agents at any time in the past were excluded from the study.

Treatments

Subjects randomized to receive Atripla were instructed to take one tablet once daily on an empty stomach, preferably at bedtime. Subjects randomized to continue on their HAART regimen (stayed on baseline regimen = SBR) were instructed to continue the regimen according to the product labelling.

Objectives

To compare the effectiveness (efficacy, safety and tolerability) in subjects on the fixed dose combination to that of subjects continuing unmodified HAART as measured by the proportion of patients who maintain HIV-1 RNA <200 copies/mL on their original assigned regimen at Week 48 using the time to loss of virologic response (TLOVR) analysis.

Outcomes/endpoints

Primary endpoint is the proportion of patients who maintain HIV-1 RNA <200 copies/mL on their originally assigned regimen at Week 48 using the time to loss of virologic response (TLOVR) analysis. Among several secondary endpoints there are the proportions of patients with HIV-1 RNA <50 copies/mL at Weeks 24 and 48, the safety and tolerability of each treatment arm, the change from

baseline in absolute CD4 cell count, viral genotypic analysis at time of virologic rebound and the change in treatment adherence.

Sample size

A total of 300 patients were enrolled.

Randomisation

Randomization was equally stratified by the use of Protease Inhibitor (PI) or Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) in the treatment regimen at study entry. Each stratum was planned to enrol approximately 150 patients and was randomized (2:1) to receive treatment arm 1 (switch to Atripla) or treatment arm 2 (SBR=unchanged HAART).

Statistical methods

A two-sided 95% confidence interval based on the difference in treatment group response rate (SBR minus continue unmodified HAART) was constructed. The confidence interval was stratified by PI- or NNRTI-based therapy. The definition of non-inferiority was employing a delta of 0.15. The Atripla arm was declared non-inferior to the SBR arm if the lower confidence limit is greater than -15%. A superiority test was performed if the lower bound of the stratified confidence interval was greater than 0. The time to event analysis was also estimated using Kaplan-Meier method. Treatment groups were tested for a group difference using the log-rank test. The 95% CI was calculated for the difference in proportion of patients with plasma HIV-1 RNA <200 copies/mL or <50 copies/mL at Weeks 24 (NB: 48-week data to be reported as follow-up measure).

RESULTS

Baseline data

The patient population was balanced for baseline characteristics, with the majority of patients being male (88%) and having a mean age of 42 years. 67% of the patients are white, 29% black and 23.3% have a hispanic/Latino origin.

Although the inclusion criterion was HIV1-RNA ≤ 200 copies/ml, the vast majority of patients (96%) had < 50 copies/ml at baseline and can thus be considered virologically suppressed also in a strict sense. The HAART regimens at study randomization are displayed in Table 8.

Table 8 Previous and Current Antiretroviral Medications (ITT Analysis Set)

Total / Most Frequent[a]	Treatment Group		
	Atripla (N = 203)	SBR (N = 97)	Total (n = 300)
Total NNRTI Regimens	**95 (47%)**	**45 (46%)**	**140 (47%)**
EFV + AZT/3TC	35 (17%)	12 (12%)	47 (16%)
EFV + ABC/3TC	11 (5%)	6 (6%)	17 (6%)
EFV + 3TC + TDF	8 (4%)	7 (7%)	15 (5%)
NVP + AZT/3TC	11 (5%)	2 (2%)	13 (4%)
EFV + 3TC + ddI	6 (3%)	2 (2%)	8 (3%)
Total PI Regimens	**108 (53%)**	**52 (54%)**	**160 (53%)**
ATV/r + FTC/TDF	30 (15%)	9 (9%)	39 (13%)
LPV/r + FTC/TDF	15 (7%)	4 (4%)	19 (6%)
NFV + AZT/3TC	9 (4%)	4 (4%)	13 (4%)
FPV/r + ABC/3TC	9 (4%)	3 (3%)	12 (4%)
FPV/r + FTC/TDF	3 (1%)	7 (7%)	10 (3%)
LPV/r + AZT/3TC	7 (3%)	2 (2%)	9 (3%)

3TC = lamivudine, ABC = abacavir, AZT = zidovudine, ddI = didanosine, EFV = efavirenz, FPV = fosamprenavir, FTC = emtricitabine, LPV = lopinavir, NFV = nelfinavir, NVP = nevirapine, r = ritonavir, TDF = tenofovir DF

a ≥ 3% of total study population

3 patients in the Atripla group were on dual antiretroviral therapy only and 6 patients in the SBR groups are treated with unboosted FPV or ATV. Of interest for the extrapolation of the results to clinical practice the previous treatments were well balanced with regard to PI and NNRTI use. Moreover, the treatment groups were also balanced with respect to prior treatment with any of the components of Atripla. Prior treatment with the triple combination was not permitted.

Outcomes and estimation

The final data from the 24-week interim analysis was provided during the assessment of the Marketing Authorisation (Tables 9 and 10); the full 48-week data is requested by the CHMP to be submitted as follow-up measure post licensure.

Table 9 Subjects with HIV-1 RNA < 50 copies/mL (ITT Analysis Set)

Endpoint, n/N (%)	Treatment Group		Difference Atripla – SBR (95% CI)
	Atripla (N = 203)	SBR (N = 97)	
PVR (KM%)	196/203 (96.5%)	94/97 (96.8%)	–0.4% (–4.7% to 4.0%)
M=Excluded	189/190 (99.5%)	88/92 (95.7%)	3.8% (0.2% to 9.9%)
M=Failure	189/203 (93.1%)	88/97 (90.7%)	2.4% (–4.0% to 10.3%)
LOCF	199/203 (98.0%)	93/97 (95.9%)	2.2% (–1.9% to 8.2%)

PVR(KM): Pure virologic response assessed using the Kaplan Meier (KM) method
M: Missing
LOCF: Last observation carried forward

Table10 Exploratory Analyses of Subgroups of Subjects (based on HAART regimen at Study Randomization) with HIV-1 RNA < 50 copies/mL (ITT Analysis Set)

		Treatment Group		Difference
	Endpoint, n/N (%)	Atripla (N = 203)	SBR (N = 97)	Atripla – SBR (95% CI)
PI Based Regimen	PVR (KM%)	102/108 (94.4%)	49/52 (94.1%)	0.3% (-7.5% to 8.1%)
	M=Excluded	100/100 (100%)	47/50 (94.0%)	6.0% (0.7% to 16.6%)
	M=Failure	100/108 (92.6%)	47/52 (90.4%)	2.2% (-6.7% to 13.8%)
	LOCF	105/108 (97.2%)	49/52 (94.2%)	3.0% (-3.7% to 13.2%)
NNRTI Based Regimen	PVR (KM%)	94/95 (98.9%)	45/45 (100%)	-1.1% (-3.4% to 1.1%)
	M=Excluded	89/90 (98.9%)	41/42 (97.6%)	1.3% (-4.6% to 11.1%)
	M=Failure	89/95 (93.7%)	41/45 (91.1%)	2.6% (-6.6% to 15.0%)
	LOCF	94/95 (98.9%)	44/45 (97.8%)	1.2% (-4.4% to 10.4%)
TDF Based Regimen	PVR (KM%)	69/74 (93.2%)	38/39 (97.4%)	-4.1% (-11.8% to 3.5%)
	M=Excluded	68/68 (100%)	35/38 (92.1%)	7.9% (0.7% to 21.4%)
	M=Failure	68/74 (91.9%)	35/39 (89.7%)	2.1% (-8.9% to 16.4%)
	LOCF	71/74 (95.9%)	36/39 (92.3%)	3.6% (-6.0% to 16.6%)
Non-TDF Based Regimen	PVR (KM%)	127/129 (98.4%)	56/58 (96.5%)	1.9% (-3.4% to 7.1%)
	M=Excluded	121/122 (99.2%)	53/54 (98.1%)	1.0% (-3.3% to 8.6%)
	M=Failure	121/129 (93.8%)	53/58 (91.4%)	2.4% (-5.3% to 12.8%)
	LOCF	128/129 (99.2%)	57/58 (98.3%)	0.9% (-3.2% to 8.1%)

For none of the analyses presented in table 10 the lower boundary of the 95%CI exceeds 7%. This data tend to show that Atripla's efficacy at 24 weeks can be considered non-inferior to SBR in patients being virologically suppressed on their baseline regimen. Analyses applying HIV1-RNA thresholds of 200 and 400 copies/ml support this conclusion.

- Analysis performed across trials (pooled analyses and meta-analysis)

For substantiating tenofovirs efficacy irrespective from its instruction for use (either with food or without food) a cross-study comparison between studies GS-01-934 and study GS-99-903 was performed. The latter was a phase 3, randomized, double blind, multicenter study of the treatment of antiretroviral-naïve HIV-1 infected patients comparing tenofovir DF administered in combination with lamivudine and efavirenz versus stavudine, lamivudine, and efavirenz (each taken according to the instructions for use as detailed in the respective SmPCs). Since lamivudin, in principle, can be considered very similar to emtricitabine, the results of this study could be compared to study GS-01-934. The virological response rates are displayed in Table 11.

Table 11 Cross study comparison; study GS-01-934 and study GS-99-903 Response rates by week 48 and week 96 (ITT Analysis Sets, missing=failure)

Study No.	GS-01-934	GS-99-903
Week 48		
N	255	299
HIV RNA < 400 copies/ml	207 (81%)	259 (87%)
HIV RNA < 50 copies/ml	194 (80%)	2228 (76%)
Week 96		
N	232*	299
HIV RNA < 400 copies/ml	173 (75%)	244 (82%)
HIV RNA < 50 copies/ml	156 (67%)	232 (78%)

*MITT-analysis set, excluding patients with baseline NNRTI resistance and week 48 responders who did not consent to continue the study after week 48.

- Clinical studies in special populations

In Studies GS-99-903 and GS-01-934, a subset of patients who had mild renal impairment (creatinine clearance ≥ 50 ml/min to < 80 ml/min) at baseline was identified. Response rates (proportions of patients who achieved and maintained confirmed HIV-1 RNA < 400 copies/ml and < 50 copies/ml (TLOVR algorithm) through Weeks 48, 96, and 144) as well as mean increases in CD4+ cell count were similar for tenofovir DF and control regimens in patients with mild renal impairment or normal renal function.

Limited data are available for patients with HBV co-infection. In study GS-01-934, no emergence of HBV mutations that could be associated with emtricitabine + tenofovir DF therapy or lamivudine/zidovudine therapy was observed through week 48 in the small subset of patients co-infected with HIV and HBV. In Study GS-99-903, 11 patients co-infected with HIV-1 and HBV (5 in the tenofovir DF group and 6 in the control group) with baseline serum HBV DNA ≥ 6 $\log_{10}$ copies/ml and with Week 48 data were analyzed. Of the 11 co-infected patients, 2 of 5 in the tenofovir DF group and 4 of 6 in the active control group discontinued prior to Week 144. One co-infected patient in the active control group died before Week 144. All patients (5/5) in the control group with HBV DNA > 1000 copies/ml developed lamivudine-resistance mutations by week 96.

- Supportive study

Study GS-98-902 was a dose-finding study for Viread comparing the efficacy of a 150 mg and 300 mg dose of TDF. The study was provided to substantiate the lack of a clinical relevant effect when the bioavailability of tenofovir DF is reduced by 35%. However, this study - also considering additional post-hoc/ad hoc analysis - could not support the intended claim.

Clinical safety

- Patient exposure

A substantial body of safety data is available from the individual active substances and in particular the post-marketing experience with the respective medicinal products. Furthermore, post-marketing data is available for Atripla itself. The cumulative patient exposure data are summarized in Table 12.

Table 12 Estimated patient exposure to the individual medicinal products

Agent	Period	Patient-Years
Efavirenz (Sustiva, Stocrin)	Cumulative to 16 September 2006	1,045,258
Emtricitabine (Emtriva)	Cumulative to 30 June 2006	52,177
Tenofovir DF (Viread)	Cumulative to 30 April 2006	714,719
Tenofovir DF/Emtricitabine (Truvada)	Cumulative to 31 July 2006	206,516
Tenofovir DF/Emtricitabine/Efavirenz (Atripla) (Truvada)	Cumulative to 31 March 2007	33,000

The single-dose bioequivalence trial GS-US-177-0105 in healthy volunteers and the uncontrolled extension phase of study GS-US-01-934 in HIV-infected patients have been performed with the intended commercial formulation of Atripla. Moreover, limited safety information is available from an ongoing study in about 200 patients being treated with Atripla (AI266073, 24-week limited data presented). Other safety data on the co-administration of the three drugs have been collated in study GS-01-934, where efavirenz, emtricitabine, and tenofovir DF have been administered as single agents (week-144 study report) and in the uncontrolled 'switch' study' GS-164-0107.

The following summarises the safety data from study GS-US-01-934 which is considered as the most relevant for the specific assessment of the fixed dose combination and its use in the intended patient population. This safety data is therefore also presented in section 4.8 of the SmPC.

Study GS-01-934

Week 144 safety analysis set

- Adverse events

The most frequently reported adverse events and adverse reactions (at least possible relationship to study drug/study regimen) are displayed in tables 13 and 14.

Table 13 Treatment-emergent adverse events reported in at least 5% of patients in either treatment group, possibly or probably related to study drugs

AE Possibly or Probably Related to Study Drugs[a] by System Organ Class and Preferred Term[b]	EFV + FTC + TDF (N = 257)		EFV + AZT/3TC (N = 254)	
	n	%	n	%
Any Related AE	86	33%	130	51%
Blood and Lymphatic System Disorders				
Anemia (including Haemoglobin Decreased)	0	0%	17	7%
Gastrointestinal Disorders				
Diarrhoea	18	7%	20	8%
Nausea	32	12%	65	26%
Vomiting	7	3%	20	8%
General Disorders and Administration Site Conditions				
Fatigue	8	3%	14	6%
Nervous System Disorders				
Headache	9	4%	13	5%

a TDF, FTC, or AZT/3TC
b Each subject counted only once per treatment and preferred term

Table 14 The most frequently reported treatment-emergent AEs with an at least possible relationship to study regimen (> 5% of patients in either treatment group)

AE Possibly or Probably Related to Study Regimen[a] by System Organ Class and Preferred Term[b]	EFV + FTC + TDF (N = 257)		EFV + AZT/3TC (N = 254)	
	n	%	n	%
Any Related AE	177	69%	193	76%
Blood and Lymphatic System Disorders				
Anemia (including Haemoglobin Decreased)	0	0%	17	7%
Gastrointestinal Disorders				
Diarrhoea	19	7%	20	8%
Nausea	46	18%	69	27%
Vomiting	8	3%	21	8%
General Disorders and Administrative Site Conditions				
Fatigue	21	8%	25	10%
Nervous System Disorders				
Somnolence	16	6%	16	6%
Headache	17	7%	19	7%
Dizziness	63	25%	66	26%
Psychiatric Disorders				
Insomnia	20	8%	23	9%
Euphoric Mood	12	5%	9	4%
Abnormal Dreams	44	17%	34	13%
Skin and Subcutaneous Tissue Disorders				
Rash	23	9%	19	7%

a EFV, TDF, FTC, or AZT/3TC b Each subject counted only once per treatment and preferred term

- Serious adverse event/deaths/other significant events

Renal and urinary disorders

One case of haematuria (1540.1088), for which the onset was on Day 1, was of Grade 1 severity; the event was considered related to study drugs and resolved on study Day 143 with no change in study drug dosing.

Table 15 Renal and Urinary Disorders Reported in > 1 Subject in Either Treatment Group

Renal and Urinary Disorders by Preferred Term[a]	EFV + FTC + TDF (N = 257)		EFV + AZT/3TC (N = 254)	
	n	%	n	%
Polakiuria (all grade 1, none related to study regimen)	1	< 1%	2	< 1%
Nephrolithiasis (none considered related to study regimen)	4*	2%	2	< 1%
Haematuria	3+	1%	0	0%

a Each subject was counted only once per treatment and preferred term.
* two reported as SAEs
+ one considered related to study regimen (see text below)

In addition to the events summarized in Table 15, acute renal failure was reported for one patient in the lamivudine/zidovudine group. The event began on Day 6, while the subject was hospitalized for an SAE of cryptococcal meningitis and was resolved on Day 13 without any change in study regimen dosing. The event was Grade 1 in severity, was not reported as an SAE, and was considered by the

investigator as unrelated to study regimen. No subject in the emtricitabine + tenofovir DF group had acute renal failure.

Statistically significant differences for mean changes from baseline in calculated creatinine clearance (Cockroft-Gault method) were reported for the two treatment groups at week 144 (-8.29 [TDF/FTC] vs. -0.56 [lamivudine/zidovudine]). Also the comparison of the glomerular filtration rate (MDRD-equation) disfavoured the TDF/FTC-group.

Other events

Bone fractures were generally trauma-related and occurred less commonly in the emtricitabine + tenofovir DF group (6 events) compared with the lamivudine/zidovudine group (8 events). They were thus not indicative of bone toxicity associated with tenofovir DF.

Skin hyperpigmentation was reported in 15 patients in the emtricitabine + tenofovir DF group and in 9 patients in the lamivudine/zidovudine group. All hyperpigmentation events, except one Grade 2 event in each treatment group, were of Grade 1 severity.

Numbers of patients with AEs related to mitochondrial toxicity are small showing no clear difference in reporting rates in either group (Table 16).

Treatment effects on body composition favoured the emtricitabine + tenofovir DF group, as evidenced by increases in mean body composition in limb fat (+1.13 kg change from Week 48 to Week 144, $p < 0.001$) compared with decreases in the lamivudine/zidovudine group (-1.09 kg change from Week 48 to Week 96, $p = 0.001$).

Five deaths occurred; however, none was reported as being related to study drug.

Table 16 Summary of Treatment-emergent Adverse Events Related to Mitochondrial Toxicity

AEs Related to Mitochondrial Toxicity by Preferred Term[a]	EFV + FTC + TDF (N = 257)		EFV + AZT/3TC (N = 254)	
	n	%	n	%
Any AE Related to Mitochondrial Toxicity	9	4%	7	3%
Peripheral Neuropathy	4	2%	2	< 1%
Acquired Lipodystrophy/Lipoatrophy/Fat Atrophy	2	< 1%	3	1%
Neuropathy	2	< 1%	0	0%
Pancreatitis/Acute Pancreatitis	1	< 1%	1	< 1%
Metabolic Acidosis	0	0%	1	< 1%
Lactic Acidosis	0	0%	0	0%
Hepatic Steatosis	0	0%	0	0%

a Each subject counted only once per treatment and preferred term

Laboratory findings

The statistically significant differences in total cholesterol and LDL-cholesterol, reported up to week 96 were no longer present at week 144.

- Discontinuation due to adverse events

Discontinuation for adverse events occurred in 13 patients in the TDF/FTC group (mainly for psychiatric disorders, drug eruption, nausea) and in 29 in the lamivudine/zidovudine group (in most cases for anaemia).

Week 24 of uncontrolled extension data set

- Adverse events

Treatment-emergent adverse events after 24 weeks of treatment with Atripla reported in the uncontrolled extension phase of study GS-US-01-934 are detailed in Table 17.

Table 17 Treatment-emergent adverse events reported in at least 5% of subjects after 24 Weeks of Atripla Treatment (Atripla Safety Subjects)

Adverse Events[a] by System Organ Class, High Level Term, and Preferred Term, n (%)	Subjects Receiving Atripla		
	Original Study Treatment Group		All Atripla
	EFV + FTC + TDF (N = 160)	EFV + AZT/3TC (N = 126)	(N = 286)
Subjects Experiencing Any AE	98 (61%)	77 (61%)	175 (61%)
Gastrointestinal Disorders	12 (8%)	17 (13%)	29 (10%)
Diarrhoea (Excl Infective)	6 (4%)	8 (6%)	14 (5%)
Diarrhoea	6 (4%)	8 (6%)	14 (5%)
General Disorders and Administration Site	9 (6%)	4 (3%)	13 (5%)
Infections and Infestations	51 (32%)	35 (28%)	86 (30%)
Upper Respiratory Tract Infections	36 (23%)	9 (7%)	45 (16%)
Nasopharyngitis	18 (11%)	4 (3%)	22 (8%)
Upper Respiratory Tract Infection	12 (8%)	4 (3%)	16 (6%)
Musculoskeletal and Connective Tissue	12 (8%)	6 (5%)	18 (6%)
Nervous System Disorders	7 (4%)	10 (8%)	17 (6%)
Psychiatric Disorders	13 (8%)	13 (10%)	26 (9%)
Disturbances in Initiating and	7 (4%)	6 (5%)	13 (5%)
Insomnia	7 (4%)	6 (5%)	13 (5%)
Skin and Subcutaneous Tissue Disorders	10 (6%)	15 (12%)	25 (9%)
Respiratory, Thoracic and Mediastinal	15 (9%)	6 (5%)	21 (7%)

a Each subject is counted only once per treatment and preferred term. AEs are classified according to MedDRA Version 9.1.

- Serious adverse event/deaths/other significant events

Five patients experienced SAEs; none of which was considered related to study drug.

One patient died due to cardiac arrest. The event was considered not related to Atripla.

- Laboratory findings

A total of 199 subjects had treatment-emergent laboratory abnormalities reported during the first 24 weeks of treatment with Atripla. No subject discontinued Atripla due to laboratory abnormalities. Treatment-emergent Grade 3 and 4 laboratory abnormalities were reported for 18 subjects (see Table 18). One subject from each of the initial treatment groups, reported a Grade 4 laboratory abnormality while receiving Atripla (hypernatriaemia, creatine kinase increased).

Table 18 Grade 3 and 4 treatment-emergent laboratory abnormalities reported after 24 Weeks of Atripla Treatment (Atripla Safety Subjects)

Grade 3 and 4 Laboratory Abnormalities, n (%)	Subjects Receiving Atripla		
	Original Study Treatment Group		All Atripla
	EFV + FTC + TDF (N = 160)	EFV + AZT/3TC (N = 126)	(N = 286)
Subjects Experiencing Any Grade 3 or 4	8 (5%)	10 (8%)	18 (6%)
Creatine Kinase Increased	2 (1%)	5 (4%)	7 (2%)
Hypertriglyceridemia	1 (< 1%)	2 (2%)	3 (1%)
Neutropenia	2 (1%)	0	2 (< 1%)
Hyperglycemia	1 (< 1%)	1 (< 1%)	2 (< 1%)
Hematuria	0	2 (2%)	2 (< 1%)
ALT Increased	1 (< 1%)	0	1 (< 1%)
Lipase Increased	1 (< 1%)	0	1 (< 1%)
Hypernatremia	1 (< 1%)	0	1 (< 1%)
Hypophosphatemia	0	1 (< 1%)	1 (< 1%)

Available safety data from the other clinical studies can be summarised as follows:

Study GS-US-177-0105

The most frequently reported adverse reactions from study GS-US-177-0105 are displayed in table 19.

Table 19 Treatment-emergent adverse events reported for at least 5% of subjects by treatment (safety analysis set)

Adverse Events[a] by System Organ Class and Preferred Term	Test Treatment[b]		Reference Treatment[c]	
	N	%	n	%
Any Adverse Event	21	46.7%	25	52.1%
Total Number of Adverse Events	114	NA	80	NA
Nervous System Disorders	16	35.6%	17	35.4%
Headache	10	22.2%	10	20.8%
Dizziness	8	17.8%	9	18.8%
Hypoesthesia	3	6.7%	0	0%
Gastrointestinal Disorders	11	24.4%	13	27.1%
Nausea	3	6.7%	4	8.3%
Diarrhea	4	8.9%	0	0%
Abdominal pain	3	6.7%	0	0%
Abdominal pain, lower	3	6.7%	0	0%
Lip dry	0	0%	3	6.3%
Musculoskeletal and Connective Tissue Disorders	7	15.6%	3	6.3%
Myalgia	3	6.7%	0	0%
Respiratory, Thoracic, and Mediastinal Disorders	5	11.1%	3	6.3%
Pharyngolaryngeal pain	3	6.7%	1	2.1%
Dyspnea	4	8.9%	0	0%

a Each subject is counted only once for each system organ class and adverse event preferred term. Adverse events mapped according to MedDRA version 8.1.

b Test Treatment = EFV/FTC/TDF fixed-dose triple-combination tablet

c Reference Treatment = EFV + FTC + TDF taken concurrently under fasted conditions

Two pregnancies (i.e. serious adverse events) occurred during the study; they were detected during period 1 (both in reference group) and ended in spontaneous abortions. The abortions were considered related to study drug by the investigators.

Several laboratory values were outside the normal range. Clear differences between the dosing groups occurred with respect to ALT (>ULN), glucose (>ULN), sodium (<LLN), and haemoglobin (<LLN), each with higher rates in the test group.

Study GS-164-0107

Treatment-emergent AEs were reported in 49% of subjects.

Grade 3 or 4 AEs were reported by 4% of subjects (17/402), none of which was reported for more than 1 subject. Grade 3 or 4 AEs reported for 1 subject each (< 1%) were thrombocytopenia, adrenal mass, pyrexia, appendicitis, injection-site cellulitis, penile abscess, pneumonia, alcohol poisoning, joint injury, meniscus lesion, multiple-drug overdose, non-insulin-dependent diabetes mellitus, flank pain, renal cell carcinoma, cerebral sarcoidosis, peripheral neuropathy, spontaneous abortion, anxiety disorder, depression. One SAE (Grade 3 thrombocytopenia) was reported as related to study drug. The patient was hospitalized and received a platelet transfusion.

Change from baseline to Week 24 for median serum creatinine concentration was 0.1 mg/dl and for median calculated creatinine clearance (Cockcroft-Gault formula) was −7 ml/min, which was statistically significant (< 0.001). None of these changes were reported as an AE, and no subject discontinued or interrupted study drug because of a renal event. Graded serum creatinine laboratory abnormalities (Grade 1 or 2) were recorded for 5 subjects.

Three subjects reported a single bone fracture, all of which were assessed by the investigator as not related to study drugs.

Treatment-emergent AEs were the cause of study drug discontinuation for 2% of subjects.

One death occurred during the study. The patient committed suicide by multiple drug overdoses. The subject had pre-existing depression, which was contributory.

Study AI266073

24-week interim data is available for this study. 12 subjects have experienced serious adverse events (SAEs) after randomization in this study (two subjects have had two separate SAEs reported). Two SAEs were considered related to study drug (Atripla: acute hepatitis and acute pancreatitis). Nine subjects (Atripla group) have experienced 19 adverse events (AEs) related to study drug that led to study discontinuation.

No further structured safety data have been provided.

- Safety in special populations

Clinical studies of efavirenz, emtricitabine, or tenofovir DF did not include sufficient numbers of elderly subjects (i.e., aged ≥ 65 years) to allow evaluation of efficacy and safety in this population. Similarly, the pharmacokinetics of efavirenz, emtricitabine, and tenofovir DF has not been evaluated in patients ≥ 65 years. Since elderly patients are more likely to have decreased renal function, the EFV/FTC/TDF fixed dose combination tablet should be used with caution when treating patients over the age of 65 years.

The EFV/FTC/TDF fixed-dose combination tablet is not recommended for use in children or adolescents (< 18 years) due to insufficient efficacy and safety data in this population, and the inability to adjust dose or dose interval.

Tenofovir and emtricitabine pharmacokinetics were substantially altered in subjects with moderate and severe renal impairment. Patients with creatinine clearance < 50 ml/min should not receive the EFV/FTC/TDF fixed-dose combination tablet. Patients with this degree of renal impairment require dose interval adjustment of emtricitabine and tenofovir DF that cannot be achieved with the EFV/FTC/TDF fixed-dose combination tablet. Increasing the dosing interval for renally impaired patients, as instructed in the Viread and Truvada SmPCs, would reduce exposure to efavirenz because its elimination is not affected by renal impairment.

- Post marketing experience

Postmarketing safety data indicate that tenofovir DF therapy may cause renal adverse reactions, including renal failure, Fanconi syndrome, and other proximal tubulopathies. The risk of such events may be increased in patients with underlying renal impairment. Moreover, the use of the EFV/FTC/TDF fixed-dose combination tablet should be avoided with concurrent or recent use of a nephrotoxic agent.

Although the postmarketing data are limited, hepatitis flares, or possible signs and symptoms of hepatitis flares, have been observed following withdrawal of treatment with tenofovir DF in patients coinfected with HBV (8 cases). Four of these occurred in HIV and HBV coinfected patients; one resulted in a fatal outcome. The remaining four cases involved off-label use for HBV mono-infection. There have been no reports of post-treatment flares during the post-marketing experience with emtricitabine.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 20 Summary of the risk management plan

Safety issue	Drug	Proposed pharmacovigilance activities	Proposed risk minimisation activities
I. Specific for the fixed combination			
Important Potential Risks			
Lack of efficacy	Atripla	Planned clinical study (non-inferiority efficacy and safety study) Ongoing clinical studies (GS-01-934, AI266-073) Observational studies (Kaiser cohort [US], Chelsea and Westminster cohort [UK])	N/A

Overdose (occurring through accidental concurrent use of Atripla with any of its active components)	Atripla	Regular analysis of postmarketing safety data	Warning in Section 4.4 of proposed Atripla SmPC
Important Missing Information			
Safety information for Atripla	Atripla	Regular analysis of postmarketing safety data GS-01-934, AI266-073, Planned clinical study (non-inferiority efficacy and safety study)	N/A
II. To address renal safety concerns			
Important Identified Risks			
Appropriate management of patients (including dosing of tenofovir DF in patients with abnormal renal function)	TDF	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data	Statements in section 4.2 and Warning in Section 4.4 of Viread, Truvada and proposed Atripla SmPCs Educational initiatives; Communications via published literature and conference presentations
Off-label use of tenofovir DF in children aged < 18 years (risk of overdose and associated increased risk of renal toxicity)	TDF	Regular analysis of postmarketing safety data Observational study in UK CHIPS cohort)	Warning in Section 4.4 of Viread SmPC
Concurrent use of Viread/Truvada/Atripla (risk of overdose and associated increased risk of renal toxicity)	TDF	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data	Warning in Section 4.4 of Viread, Truvada and proposed Atripla SmPCs
Events resulting from tenofovir DF renal toxicity: bone (osteomalacia), muscle (myopathy)	TDF	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data Clinical studies in children (GS-US-104-0321, GS-US-104-0352)	Listed as ADRs in Section 4.8 of Viread, Truvada and proposed Atripla SmPCs
Important Potential Risks			
Reversibility of tenofovir DF renal toxicity (possible long-term damage)	TDF	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data Study GS-US-104-0353	N/A
Fatal outcome	TDF	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data	N/A

Other events which may be caused by tenofovir DF renal toxicity: bone (including fractures), muscle (including rhabdomyolysis), cardiac events	TDF	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data Clinical studies in children (GS-US-104-0321, GS-US-104-0352) Study ACTG 5202	N/A
Important Missing Information			
Incidence of tenofovir DF renal toxicity	TDF	Observational studies in adults (EuroSIDA, Kaiser and NADIS Cohort Studies)	Communication of findings concerning renal toxicity through publication in the scientific literature and conferences. Update of labeling and educational program as appropriate
Risk factors for tenofovir DF renal toxicity	TDF	Enhanced follow up of postmarketing adverse event reports (to generate hypotheses which can be assessed formally in observational studies) Regular analysis of postmarketing safety data Observational studies (EuroSIDA, Kaiser and NADIS Cohort Studies) Study GS-US-104-0352	As above
Genetic pre-disposition to tenofovir DF renal toxicity	TDF	Pharmacogenomics study (under discussion)	As above
Mechanism of tenofovir DF renal toxicity	TDF	Nonclinical Studies (Renal Transporters/ Intestinal Absorption studies)	As above
Safety and efficacy of dosing recommendations in HIV patients with renal impairment	TDF	Regular analysis of postmarketing safety data	As above
Renal safety profile in pediatric and elderly patients	TDF	Regular analysis of postmarketing safety data Clinical studies in children (GS-US-104-0321, GS-US-104-0352) Observational study in UK (CHIPS cohort)	As above
III. To address other safety concerns			
Important Identified Risks			
Psychiatric and nervous system symptoms	EFV	Regular analysis of postmarketing safety data	Warning in Section 4.4 of Sustiva/Stocrin and proposed Atripla SmPCs ADRs listed in Section 4.8 of Sustiva/Stocrin and proposed Atripla SmPCs

Skin rash and skin reactions	EFV	Regular analysis of postmarketing safety data	Warning in Section 4.4 of Sustiva/Stocrin and proposed Atripla SmPCs ADRs listed in Section 4.8 of Sustiva/Stocrin and proposed Atripla SmPCs
Hepatic enzyme elevation	EFV	Regular analysis of postmarketing safety data Clinical study (pharmacokinetics of efavirenz in subjects with selected degrees of hepatic impairment, AI266917) Epidemiological study (D:A:D cohort study of liver related death in patients with HIV infection who are co-infected with HBV/HCV)	Contraindication for patients with severe hepatic impairment in Section 4.3 and Warning in Section 4.4 of Sustiva/Stocrin and proposed Atripla SmPCs
Potential association with neural tube abnormalities	EFV	Regular analysis of postmarketing safety data Epidemiological study (Antiretroviral Pregnancy Registry)	Advisory statements in Section 4.6 of Sustiva/Stocrin and proposed Atripla SmPCs Prominent wording in proposed Atripla PIL Medical Information Enquiries (Pregnancy letter)
Post-treatment hepatic flares in HIV/HBV co-infected patients	FTC and TDF	Regular analysis of postmarketing safety data	Warning in Section 4.4 of Viread, Truvada and proposed Atripla SmPCs
Interaction with didanosine	TDF	Regular analysis of postmarketing safety data	Warning in Section 4.4 and interaction described in Section 4.5 of Viread, Truvada and proposed Atripla SmPCs
Important Potential Risks			
Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms	EFV	Regular analysis of postmarketing safety data	Statements under 'Biotranformation' in Section 5.2 of Sustiva/Stocrin (EC decision 23 August 2007) and proposed Atripla SmPCs
Bone fractures/loss of bone density	TDF	Regular analysis of postmarketing safety data Clinical studies (long term safety studies – GS-99-903 and GS-01-934, ACTG 5202)	Warning in Section 4.4 of Viread, Truvada and proposed Atripla SmPCs
Important Missing Information			
Safety in children (see also Renal Safety Concern for TDF above)	EFV and TDF	Regular analysis of postmarketing safety data Clinical Studies (EFV – AI266922; TDF – GS-US-104-0321, PACTG P1053, GS-US-104-0352)	Statements in section 4.2 of Viread, Truvada, Sustiva/Stocrin and proposed Atripla SmPCs Warning in Section 4.4 of Viread and Sustiva/Stocrin SmPCs

Safety in elderly patients (see also Renal Safety Concern for TDF above)	EFV, FTC and TDF	Regular analysis of postmarketing safety data	Statements in section 4.2 of Viread, Emtriva, Truvada and proposed Atripla SmPCs Warning in Section 4.4 of Viread and Sustiva/Stocrin SmPCs
Safety in pregnancy	EFV, FTC and TDF	Epidemiological study (EFV, FTC, TDF - Antiretroviral Pregnancy Registry; FTC, TDF – Cross sectional study to assess the risk of mitochondrial disease in children exposed to NRTIs in utero [MITOC group])	Advisory statements in Section 4.6 of Sustiva/Stocrin, Viread, Emtriva, Truvada and proposed Atripla SmPCs Prominent wording in proposed Atripla PIL
Safety in patient with hepatic impairment	EFV	Regular analysis of postmarketing safety data Clinical study (pharmacokinetics of efavirenz in subjects with selected degrees of hepatic impairment, AI266917)	Contraindications for patients with severe hepatic impairment in Section 4.3 and Warning in Section 4.4 of Sustiva/Stocrin and proposed Atripla SmPCs

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, the development of a suitably-discriminating dissolution test for all active substances was considered to require further improvement. This issue together with a few minor unresolved quality issues, which all do not have any impact on the benefit/risk ratio of the medicinal product, will be addressed as part of the follow-up measures to be addressed post-authorisation.

Non-clinical pharmacology and toxicology

The non-clinical study programme for the fixed combination reflects that all individual components are already approved for antiretroviral combination therapy. Due to the available non-clinical data for the individual compounds and the dual combination emtricitabine / tenofovir DF, as well as the sufficiently documented human experience of the combined use of all compounds, the lack of additional nonclinical studies for the fixed combination product was considered justified by the CHMP. Further toxicological investigations with the triple combination are unlikely to yield new data relevant to humans given that the preclinical toxicology profile of the individual agents is well established and no synergistic toxicities are predicted.

The pharmacodynamic assessment of efavirenz, emtricitabine and tenofovir DF appears to support the use of these 3 agents together in combination therapy for HIV-1 disease. Regarding the potential for drug resistance the use of the triple combination product, in vitro studies have shown neither cross-resistance between the NRTI-associated substitutions M184V/I and/or K65R and efavirenz nor any cross-resistance between efavirenz-associated substitutions and either emtricitabine or tenofovir. With the exception of the limited findings from Study AD-177-2001, no new pharmacokinetics studies have been conducted or reported that are relevant to EFV/FTC/TDF film-coated tablets. The toxicologic

profiles of efavirenz, emtricitabine, and tenofovir are well characterized in multiple animal species and with the exception of the limited findings from Study AD-177-2001, no other new toxicology studies have been conducted or reported that are relevant to fixed combination. All impurities and degradation products have been evaluated and qualified. There are no new impurities or degradation products. An environmental risk assessment was provided in support of the application and studies have been performed or are on going with the latter to be submitted as follow-up measure.

Efficacy

In the bioequivalence study (GS-US-177-0105) it was demonstrated that the commercial formulation of Atripla is bioequivalent to the respective co-administered individual medicinal products. However, this study was conducted in fasting conditions. According to the currently approved SmPCs for tenofovir-containing medicinal products these should be taken with food; this is because available pharmacokinetic data unequivocally demonstrates a reduction in bioavailability of tenofovir by 35% when administered without food.

The fixed dose combination Atripla, however, is recommended to be taken without food, since otherwise exposure to efavirenz would increase and thus potentially negatively impact the safety profile of the drug.

The applicant claims the absence of a clinically relevant food effect on tenofovir exposure based on pharmacokinetic/pharmacodynamic data as well as efficacy data. However, the arguments were either not appropriately substantiated or the data provided was not considered sufficient. Therefore, the CHMP raised concerns regarding the lack of clinical data to demonstrate that the reduced bioavailability of tenofovir DF has no impact on the clinical effect of the combination.

In study GS-01-934, the once-daily regimen of efavirenz, emtricitabine, and tenofovir DF administered without regard to food demonstrated durable antiviral efficacy comparable to that of a regimen containing lamivudine/zidovudine + efavirenz as well as immunological benefit in antiretroviral treatment-naive HIV-1 infected patients at week 144. The extension study post week 144, in which patients of both treatment groups completing 144 weeks were rolled-over to Atripla, was not considered appropriate for the demonstration that the reduced bioavailability of tenofovir DF when administered without food does not translate into a clinically relevant effect due to the lack of a control group, the highly pre-selected patient population, the lack of administration guidance before week 168, the short duration of therapy with Atripla as well as the lack of appropriate statistical analyses. Of note is that in this extension statistically significant differences in virologic response and CD4 cell count between week 144 and week 168 were observed. Data on "study drug intake with/without food" was collected from the participants. However, since a protocol for this part of the study was not submitted, the validity of the data has to be questioned.

Similarly, results of study GS-US-164-0107 could be interpreted that in virologically controlled, treatment-experienced patients, switching from the twice-daily regimen of lamivudine/zidovudine + efavirenz to a once-daily (two-tablet) regimen of emtricitabine/tenofovir DF + efavirenz was associated with maintenance of virologic suppression and immune function. However, also this study presents with major deficiencies in its design, in particular the lack of a control group. The medicinal products could be taken without regard to food; however, no data has been submitted on the proportions of patients taking it in either way.

Study GS-98-902 clearly shows that the study data does not allow concluding on non-inferiority of the two doses. The data from study GS-99-903 could be regarded as supportive at best based on the similarities between lamivudine and emtricitabine. In neither study data was collected on the actual dosing of the study drugs, i.e. if the three APIs, efavirenz, emtricitabine, and tenofovir DF were all taken at the same time.

Finally, study AI266073 may not serve as a proof for non-inferiority of Atripla as compared with the individuals agents due to the exclusion of patients with efavirenz, emtricitabine and tenofovir DF in their current antiretroviral regimen with the consequence that this study may not contribute to clarification of the issue whether the intake of tenofovir DF without food (when given as Atripla) will

impact the efficacy of this triple combination therapy. However, when specifically considering a switch in virologically suppressed patients then the study results appear promising. The vast majority of patients had a successful virologic suppression at baseline and maintained it, even when applying the threshold of 50 copies/ml. The lower boundary of the 95% confidence interval did not exceed -5% in any of the main analyses. Overall, at 24 weeks the results are compatible with the hypothesis of non-inferiority between Atripla and continuing HAART, when applying a non-inferiority margin of 7%.

Safety

Extensive post-marketing data has been collated for the three active substances contained in Atripla. Limited safety data for the fixed combination itself in patients has been presented (clinical studies, post-marketing experience). In principal, the reported types and rates of adverse events from these data sets are compatible with the already known adverse event profiles of the individual components, also with respect to the adverse events of special interest. Special safety concerns known for the individual active substances are CNS toxicity and rash (efavirenz), renal and bone toxicity (tenofovir DF), as well as hyperpigmentation and mitochondrial toxicity (emtricitabine).

In the bioequivalence study in healthy volunteers, more adverse reactions were reported for the test group, with some types of adverse reactions occurring only in subjects having taken the test formulation, e.g. hypoaesthesia, diarrhoea, abdominal pain, myalgia, and dyspnoea. Also, the documented differences in the laboratory findings between test and reference group (alterations in ALT, glucose, Na, Hb, and urinalysis) after intake of only one single dose of Atripla are noteworthy.

This study did include by majority healthy women of child-bearing potential; two pregnancies (and abortions) have been reported during this study of less than two months duration. Pregnancies with the use of Atripla are of concern given that efavirenz is an agent with marked teratogenic effects in animals hence an additional pregnancy warning was added to the product information including the recommendation to use effective dual contraceptive measures not only during therapy but also for up to 12 weeks after cessation of therapy.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

User consultation

A readability testing (user consultation) of the package leaflet for Atripla 600 mg/ 200 mg/ 245 mg film-coated tablets has been conducted on the English language version of the proposed package leaflet submitted in the initial application. The results of this user testing are considered acceptable and in accordance with the relevant guideline.

Risk-benefit assessment

Benefits

Atripla is a fixed-dose combination of the non nucleoside reverse transcriptase inhibitor efavirenz, the nucleoside reverse transcriptase inhibitor emtricitabine, and the nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate. The combination of these antiretroviral substances for the treatment of HIV-1 infection has shown good and durable antiretroviral efficacy in terms of virologic as well as immunologic parameters and a satisfactory safety profile in antiretroviral therapy naïve patients through 144 weeks of therapy as compared to lamivudine/zidovudine + efavirenz. It is thus generally recommended as one option in “first-line” therapy in these patients.

The individual substances as well as a dual combination of emtricitabine and tenofovir DF have already been licensed for combination antiretroviral therapy. Thus, the benefit for Atripla rests on the convenience of taking a single tablet once daily that combines three agents instead of taking two or three tablets that also have to be taken once daily, however, not at the same time due to different instructions for use (i.e. with/without food).

Risks

The development of this triple combination encounters a conflict regarding the instructions for use. While tenofovir DF is to be administered with food to increase bioavailability, it is recommended to take efavirenz on an empty stomach, since food would increase the bioavailability. An increase in systemic exposure of efavirenz, however, is considered critical especially in light of its CNS toxicity.

Due to the safety concerns with efavirenz it is recommended to follow for the fixed dose combination Atripla the same administration schedule, i.e. on an empty stomach ideally at bedtime. However, the available pharmacokinetic data on tenofovir DF demonstrates that this would reduce its bioavailability by 35%. It would hence need to be shown that this reduction in exposure does not hamper the clinical efficacy of the triple combination.

No adequate clinical data was provided to support this change of the instructions for use tenofovir DF in general. The only study which allows drawing conclusions on the efficacy of the fixed combination given on an empty stomach investigates the switch of existing HAART regimens in patients with adequate virological response to their prior treatment to Atripla.

Balance

Acknowledging the efficacy and safety of the combination of efavirenz, emtricitabine and tenofovir DF for the treatment of HIV-1 infection, the CHMP nevertheless did not consider that the convenience of "one tablet once daily" would outweigh the risk of lower efficacy due to reduced bioavailability of one of the components of the fixed dose combination. Adequate data to demonstrate the lack of clinical relevance of the unavoidable change of the administration of tenofovir TD in the fixed dose combination has not been provided. In order to confirm the assumption of a negligible impact of the food influence on the efficacy of tenofovir within the fixed dose combination, a comparative study would be needed to allow for a comparison between Atripla at fasting conditions and the individual substances administered according to their currently approved SmPCs. In the absence of this study the general use of the fixed dose combination for treatment of HIV-1 infection was not considered sufficiently justified.

However, the CHMP considered the available data for the switch in virologically suppressed patients from their successful antiretroviral combination therapy to Atripla as sufficient for concluding on non-inferiority of Atripla as compared to other continued HAART regimens in this patient population. The resulting increase in convenience due to the simplified dose regimen would constitute an adequate benefit in this case; additional data on maintenance of the virologic response over 48 weeks was requested to be provided as follow-up measure.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see as detailed in section 2.3.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Atripla in the therapeutic indication

> "Atripla is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Atripla prior to initiation of their first antiretroviral treatment regimen (see sections 4.4 and 5.1).
>
> The demonstration of the benefit of Atripla is primarily based on 24-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to Atripla (see section 5.1). No data are currently available from clinical studies with Atripla in treatment-naïve or in heavily pretreated patients.
>
> No data are available to support the combination of Atripla and other antiretroviral agents."

was favourable and therefore recommended the granting of the marketing authorisation.